CADTH

CADTH OPTIMAL USE REPORT

Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Clinical Report

PROSPERO REGISTRATION NUMBER: CRD42019119293

Service Line:	Optimal Use
Issue:	Vol. 9, No. 1c
Publication Date:	August 2019
Report Length:	192 Pages

CADTH

Cite As: *Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Clinical Report*. Ottawa: CADTH; 2019 Jul. (CADTH Optimal Use Report; vol. 9, no. 1c).

ISSN: 1927-0127

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Tables

Figures

Abbreviations

AE	adverse event
ATE	average treatment effect
CAR	chimeric antigen receptor
CI	confidence interval
CNS	central nervous system
CORAL	Collaborative Trial in Relapsed Aggressive Lymphoma
CR	complete response or complete remission
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESS	effective sample size
HR	hazard ratio
HTA	health technology assessment
ICU	intensive care unit
IPD	individual patient data
IPI	International Prognostic Index
IPW	inverse-probability weighting
IRC	Independent Central Review Committee
ITT	intention-to-treat
IWG	International Working Group
KM	Kaplan–Meier
MAIC	matching-adjusted indirect comparison
mITT	modified intention-to-treat
NCCN	National Comprehensive Cancer Network
ND	not done
NE	not estimable
NHL	non-Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PMBCL	primary mediastinal large B-cell lymphoma

PR	partial response or partial remission
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	propensity score
RCT	randomized controlled trial
r/r	relapsed or refractory
RR	response rate
SAE	serious adverse event
SCT	stem cell transplant
TFL	transformed follicular lymphoma

Protocol Amendments

Amendment	Page in Protocol Document
Following Health Canada's issue of a Notice of Compliance for axicabtagene ciloleucel and publication of the final product monograph, the confirmed indication was used to inform a revision of the indication in the population eligibility criterion for the review (i.e., instances of "non-Hodgkin lymphoma" were changed to "large B-cell lymphoma" throughout).	All (including title page and all footers)
In response to feedback on the draft report, clarification was added to the description of subgroups of interest (i.e., MYC, B-cell lymphoma 2, or B-cell lymphoma 6 gene rearrangements [double or triple hit]).	Page 11
Following the incorporation of patient input into the clinical review, outcomes of particular importance to patients were added to the outcomes of interest.	Pages 11, 12
In response to feedback on the draft report, outcomes categorized under "Safety" were re-categorized as "Other" (i.e., management of adverse effects, frequency of manufacturing failure).	Page 12
Following Health Canada's issue of a Notice of Compliance for axicabtagene ciloleucel and publication of the final product monograph, the confirmed indication was used to inform a revision to a table footnote indicating that studies reporting data from primary refractory patients would be eligible for inclusion in the review (i.e., only studies reporting data from patients who were relapsed or refractory after two lines of systemic therapy were eligible for inclusion in the clinical review). This amendment was also applicable to the study screening checklists.	Page 12, Appendix 4 (Table 2 and Table 3)

Executive Summary

Introduction

Large B-cell lymphomas include some of the most common and aggressive subtypes of non-Hodgkin lymphoma. For patients who experience relapsed or refractory (r/r) large B-cell lymphoma, there are few treatment options available, none of which produce long-term survival benefits.

Axicabtagene ciloleucel is a second-generation chimeric antigen receptor T-cell therapy that targets the CD19 antigen, expressed exclusively on B cells, including the cancer cells involved in aggressive large B-cell lymphomas. Health Canada approved axicabtagene ciloleucel in February 2019 for adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and diffuse large B-cell lymphoma arising from follicular lymphoma.

Objective

The objectives of this clinical review were to systematically evaluate the beneficial and harmful effects of axicabtagene ciloleucel for eligible types of r/r large B-cell lymphoma in adults and to identify available evidence-based guidance for the use of axicabtagene ciloleucel in this population. This project is a component of a larger CADTH health technology assessment to assess clinical effectiveness, cost-effectiveness, patient and caregiver perspectives and experiences, ethical issues, and implementation considerations.

Results and Interpretation

Search and Screening

A total of 37 reports were included that described one pivotal trial (ZUMA-1) and one clinical practice guideline for r/r large B-cell lymphoma.

Included Studies

ZUMA-1, two indirect treatment comparisons submitted by the manufacturer, and the clinical practice guideline met the inclusion criteria. ZUMA-1 is an ongoing phase I/phase II single-arm, open-label, multi-centre study, conducted in 22 centres (21 in the US and one in Israel). The clinical practice guideline was developed by the National Comprehensive Cancer Network and covered aspects of patient selection for chimeric antigen receptor T-cell therapy.

Outcomes Assessed

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

The outcomes evaluated in ZUMA-1 were objective response rate, progression-free survival, duration of response, overall survival, and harms.

Conclusion

The efficacy findings from ZUMA-1 suggest that in adults with eligible types of r/r large B-cell lymphoma, treatment with axicabtagene ciloleucel resulted in demonstrable objective response rate and favourable secondary outcomes; however, longer follow-up is needed. In addition, axicabtagene ciloleucel has the potential to exert severe adverse events. Direct comparative data will be required to fully understand the benefit–risk profile of axicabtagene ciloleucel and its place in therapy for relapsed or refractory large B-cell lymphomas.

Introduction

Clinical Need and Target Population

Lymphomas are blood cancers that develop in the lymphatic system; they are divided into Hodgkin lymphoma and non-Hodgkin lymphomas (NHLs). In Canada, NHL accounts for 83% of all cases of lymphomas.[1] NHLs are categorized as B-cell, T-cell, or natural killer/T-cell lymphoma, depending on the cell implicated in the disease.[1,2] While B-cell NHLs display a wide range of clinical behaviours, there are several subtypes that have a similar clinical course and are treated in a similar manner. These subtypes include diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Among these subtypes of NHLs, DLBCL is an aggressive variant that is also the most common.[1,3,4] Although it can occur at any age, DLBCL is the most commonly occurring subtype of NHL in adults,[5-8] accounting for 30% to 40% of all adult lymphomas,[6,7,9,10] with an estimated annual incidence of around 10.2 per 100,000. DLBCL is relatively sensitive to chemotherapy, and the complete remission rate in patients who undergo first-line chemotherapy is approximately 50% to 70%.[8,11] However, 30% to 50% of patients experience relapse and 10% have refractory (i.e., non-responsive to first-line treatment) DLBCL.[8,11] If left untreated, the life expectancy of patients with relapsed or refractory (r/r) DLBCL is three to four months.[11] Second-line (or salvage) therapy is used for DLBCL patients who do not respond to chemotherapy or who relapse after initial response.[12] The objective response rate (ORR) to salvage therapy has been reported to be 26% (7% complete response rate), with a median overall survival (OS) time of 6.3 months.[8]

PMBCL mainly affects young women and has been reported to account for approximately 2% to 4% of all lymphomas.[1] Follicular lymphoma comprises 20% of new diagnoses of NHL and often has a longer, more indolent course. The majority of patients who die of follicular lymphoma die of transformed disease, with the follicular lymphoma transforming to DLBCL at a rate of 1% to 3% per year.[13] No Canadian data were identified on the incidence and prevalence of high-grade B-cell lymphoma, and r/r cases of PMBCL, high-grade B-cell lymphoma, or DLBCL arising from follicular lymphoma.

A range of standard treatments are used as first-line or second-line therapies to treat the aggressive forms of B-cell lymphoma. Such treatments include chemotherapy, immunotherapy, radiation therapy, and autologous stem cell transplant (SCT).[1,4,14] However, these treatments fail for an estimated 20% of patients.[4] Outside of approved chimeric antigen receptor (CAR) T-cell therapies, only palliative options are currently available for patients with large B-cell lymphoma who do not respond to second-line therapy. The estimated OS for these patients is approximately six months.[4,12,14]

In this context, axicabtagene ciloleucel is a CAR T-cell therapy that has been approved by Health Canada for use in “adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.”[15]

A Brief Overview of Axicabtagene Ciloleucel

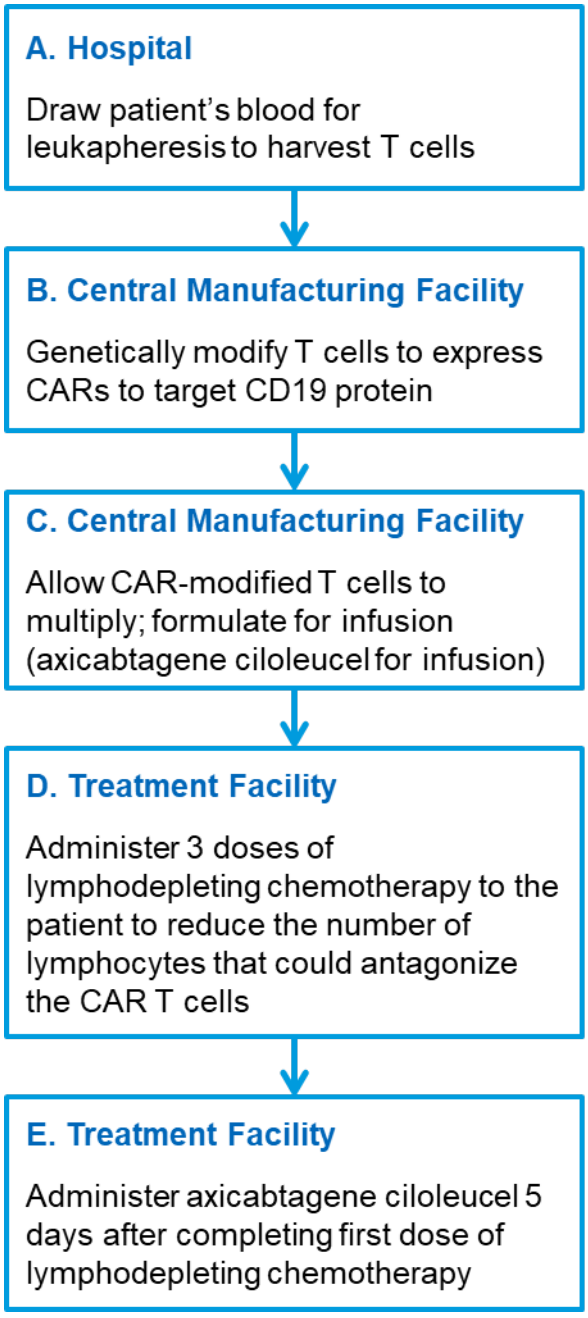
CAR T-cell therapy uses genetic engineering to alter a patient's own T cells to kill tumour cells. CARs are artificial receptors that redirect antigen specificity, activate T cells, and further enhance T-cell function through their co-stimulatory component.[16] Axicabtagene ciloleucel (brand name: Yescarta) is a second-generation CAR T-cell therapy designed to target the CD19 antigen, which is expressed on the surface of B cells, including the malignant cells involved in the aggressive B-cell NHLs.[12] The manufacturing process for axicabtagene ciloleucel involves using leukapheresis to collect the patient's peripheral blood mononuclear cells, isolating the T cells, and sending them to a central facility.[15] At the central processing facility, the DNA for the chimeric protein is inserted into the DNA of the patient's T cells using retrovirus vectors. The CAR portion in axicabtagene ciloleucel is composed of an extracellular murine, anti-CD19, single-chain, variable fragment linked to intracellular CD28 and CD3-zeta co-stimulatory domains.[15] The resulting CAR T cells are expanded in cell culture, washed, formulated into a suspension, cryopreserved, and then shipped back to the treating institution for infusion into the patient's blood stream to fight the cancer.[15] Axicabtagene ciloleucel must remain frozen until the patient is ready for treatment in order to ensure the viability of the product. An overview of the CAR T-cell therapy procedure is provided in Figure 1. Before the infusion of the CAR T cells, the patient must undergo lymphodepleting chemotherapy to decrease the number of competing unmodified lymphocytes, which enhances the engraftment and survival of the genetically modified T cells.

It is administered by intravenous infusion in a single dose. Each 68 mL patient-specific, single-infusion bag contains a suspension of anti-CD19 CAR-positive viable T cells for a target dosage of 2×10^6 CAR-positive viable T cells per kilogram of body weight (range: 1×10^6 – 2.4×10^6 cells per kilogram of body weight), with a maximum of 2×10^8 CAR-positive viable T cells, for patients of 100 kg and above.[15] Prior to receiving the infusion of axicabtagene ciloleucel, patients undergo lymphodepleting chemotherapy, with three doses (one dose per day) of cyclophosphamide and fludarabine administered via infusion on the fifth day, fourth day, and third day before infusion of axicabtagene ciloleucel.[15]

In October 2017, axicabtagene ciloleucel was the first CAR T-cell therapy to receive regulatory approval by the FDA for the treatment of adults with certain types of r/r B-cell lymphoma.[3] In August 2018, axicabtagene ciloleucel was granted approval in the European Union for the treatment of adult patients with r/r DLBCL and PMBCL, after two or more lines of systemic therapy.[17,18] In February 2019, axicabtagene ciloleucel was approved by Health Canada for adult patients with the previously described types of r/r large B-cell lymphoma after two or more lines of systemic therapy;[19] it is the second CAR T-cell therapy approved in Canada.

Given the associated high costs, the uncertainty of the clinical benefit and long-term harms, and the potential for adverse events (AEs), there is a need to critically evaluate the benefits and risks of axicabtagene ciloleucel for r/r large B-cell lymphoma prior to its implementation in Canada.

Figure 1: An Overview of Manufacturing and Administering Chimeric Antigen Receptor T-Cell Therapy (Axicabtagene Ciloleucel)



CAR = chimeric antigen receptor.

Policy Question

The health technology assessment (HTA) addresses the following policy question:

How should the provision of axicabtagene ciloleucel be structured for treating adults with eligible types of r/r large B-cell lymphoma?

Objectives

The objective of this clinical review was to assess the beneficial and harmful effects of axicabtagene ciloleucel for eligible types of relapsed or large B-cell lymphoma in adults and to identify available evidence-based guidance for the use of axicabtagene ciloleucel in this population. This project is a component of a larger CADTH HTA to assess clinical effectiveness, cost-effectiveness, patient and caregiver perspectives and experiences, ethical issues, and implementation considerations. Each component of the HTA was conducted individually and collaboratively.

Research Questions

The following clinical research questions were addressed in this review:

1. What are the beneficial effects of axicabtagene ciloleucel for treating adults with eligible types of relapsed or refractory large B-cell lymphoma?
2. What are the harmful effects of axicabtagene ciloleucel for treating adults with eligible types of relapsed or refractory large B-cell lymphoma?
3. What are the evidence-based clinical practice guidelines for the use of axicabtagene ciloleucel for the treatment of adults with eligible types of relapsed or refractory large B-cell lymphoma?

Methods

The methods for this review were informed by the criteria outlined in the AMSTAR 2 checklist.[20] The clinical review was conducted in accordance with CADTH standards for Optimal Use reviews and with relevant reporting guidelines such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and PRISMA harms statements.[21,22]

The protocol for the systematic review was developed and written a priori based on information from an informal scoping review.[23] The protocol was followed throughout the review process.

Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy. See Appendix 1 for the detailed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–), Embase (1974–), the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessment database via Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO, and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's

MeSH (Medical Subject Headings), and keywords. The main search concepts were axicabtagene ciloleucel, NHL, and CAR T-cell therapy.

No methodological filters were applied to limit the retrieval of the axicabtagene ciloleucel search by study type. This search was not limited by language or publication date. Methodological filters were applied to limit the retrieval of the NHL and CAR T-cell therapy searches to clinical practice guidelines, HTAs, systematic reviews, or meta-analyses. The search for NHL publications was limited to English- or French-language documents published between January 1, 2016, and November 2018. The search for CAR T-cell therapy publications was limited to English- or French-language documents published between January 1, 2013, and November 2018.

The search was completed in November 2018. Regular alerts were established to update the searches until the publication of the final report. Regular search updates were performed on databases that do not provide alert services. Studies identified in the alerts that met the inclusion criteria of the review and offered new analytical insight were incorporated into the review. Any studies identified after the manufacturer feedback period were described in the discussion, with a focus on comparing the results of these new studies with the results of the analyses conducted for this report.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (FDA and European Medicines Agency [EMA]), clinical trial registries (U.S. National Institutes of Health's ClinicalTrials.gov and the Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database and were not limited by publication date. Abstracts from the American Society of Hematology, the American Society of Clinical Oncology, the European Hematology Association, and the European Society for Medical Oncology were searched manually for conference years not available in Embase.

Relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters) were also searched, which includes the websites of HTA agencies, clinical guideline repositories, systematic review repositories, and professional associations. Google was used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Study Eligibility

The pivotal study conducted and provided by the manufacturer was included in the systematic review. Additional studies were included if they were published in English or French and met the criteria presented in Table 1.

Studies with mixed populations that included patients who were not included in the Health Canada–approved indications were eligible for inclusion if separate results were reported for the eligible patients. Studies with mixed populations in which the results for the population were not reported separately were eligible for inclusion if 66% or more of the population met the eligibility criteria (cut-off point based on expert opinion).

If multiple reports were identified for the same eligible study, all reports from the study were retained but only the most current or complete data were extracted. Publication status (e.g., abstracts) was not a criterion for exclusion.

Position statements and consensus documents that did not make reference to evidence upon which the recommendations are based were not included. For Canadian guidelines, national, provincial, or territorial guidelines were eligible for inclusion. For non-Canadian guidelines, only national-level guidelines were eligible for inclusion in order to account for their generalizability to the Canadian context. Guidelines that were explicitly applicable to a smaller jurisdiction or a specific facility were excluded.

Table 1: Eligibility Criteria for Clinical Research Questions

Population(s)	Adult patients (≥ 18 years) with r/r large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma[a] Subgroups of possible interest include number of previous lines of systemic therapy; subtype of lymphoma; cell of origin; age; sex; race; ECOG performance status; relapsed/refractory status; previous stem cell transplant; CAR T-cell dosage; conditioning chemotherapy; tumour burden at the time of therapy; stage of disease; histological score; MYC, BCL2 or BCL6 rearrangements (double or triple hit); EBV-positive or -negative tumour status
Intervention(s)	Axicabtagene ciloleucel[b] (Gilead Sciences) [c]
Comparator(s)	• Salvage chemotherapy • Other CAR T-cell therapies (e.g., tisagenlecleucel) • No comparator • No additional therapy
Outcome(s)	**Clinical Efficacy/Effectiveness Outcomes** • Response/remission rate[d] (e.g., objective response/remission rate, complete response, partial response)[e] • Survival (e.g., overall, event free, progression free) [e] • Persistence of CAR T cells • Health-related quality of life and other patient-reported outcomes)[e] • The need for subsequent treatment(s)[e] **Safety/Harms Outcomes** • Mortality (e.g., treatment-related mortality, all-cause mortality) • AEs, serious AEs (e.g., AEs ≥ grade 3), withdrawal due to AE • Notable harms: CRS, B-cell aplasia, febrile neutropenia, neurological effects (e.g., hallucination, dysphasia), documented infections • Development of secondary malignancy • Hospitalization (e.g., hospital readmission, length of stay, admission to the ICU)[e] **Other Outcomes** • Management of adverse effects • Frequency of manufacturing failure **Evidence-Based Clinical Practice Guidelines**[f]

Study Design(s)	**Experimental or Observational Comparative and Non-comparative Primary Studies** • RCTs • Non-randomized controlled clinical trials • Single-arm studies • Cohort studies[g] • Case-control studies • Case series[g] • Indirect treatment comparisons, network meta-analyses **Evidence-Based Clinical Practice Guidelines[f]** **Exclusions** • Case reports • Review articles • Editorials, letters, and commentaries

AE = adverse events; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; ICU = intensive care unit; RCT = randomized controlled trial; r/r = relapsed or refractory.

[a] Eligible indications included patients with relapsed (i.e., returned) or refractory (i.e., no response to treatment) large B-cell lymphoma after two or more lines of systemic therapy.

[b] A lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 is administered intravenously on the fifth day, fourth day, and third day before infusion of axicabtagene ciloleucel.

[c] The target dose of axicabtagene ciloleucel is 2 × 10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2 × 10^8 CAR-positive viable T cells in approximately 68 mL.[24] Studies in which axicabtagene ciloleucel was administered at a different dose were eligible for inclusion.

[d] "Response" and "remission" were considered synonymous in the context of this review, in accordance with the National Cancer Institute's *Dictionary of Cancer Terms* and FDA's *Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry*.[25,26]

[e] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

[f] "Clinical practice guidelines" were defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[27] Guidelines that were evidence-based (i.e., informed by supporting data or citations) and that were developed or endorsed at the national level (e.g., from national societies or federal governments) for non-Canadian guidelines, or at the national, provincial, or territorial level for Canadian guidelines, were eligible for inclusion.

[g] Cohort studies were defined as studies in which participants were compared based on whether or not they received an exposure; participants could be studied prospectively or retrospectively.[28] Case series were defined as studies in which participants were sampled on the basis of the presence of an outcome, or of both an exposure and outcome.[29] For case series studies, a minimum sample size of five patients was required to be eligible for inclusion.[30]

Literature Screening and Selection

Using the eligibility criteria outlined in Table 1, two reviewers independently screened all titles and abstracts identified through the literature searches (level I screening). Full-text articles of titles/abstracts deemed potentially relevant by at least one reviewer were retrieved for a second-level screening (of the full text). The same reviewers independently examined full-text articles to select studies for inclusion in the review. Disagreements between the reviewers were resolved through consensus. Study selection was conducted using DistillerSR online software with standardized screening forms.[31] One reviewer checked the reference lists of potentially relevant HTAs or systematic reviews for additional records of relevance, and a second reviewer confirmed eligibility as applicable.

The study selection process is outlined in a PRISMA flow chart (see Appendix 2). A list of included and excluded studies, with the reasons for exclusion, are provided in Appendix 3 and Appendix 4, respectively.

Data Extraction

Data extraction was performed by one reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved through discussion until consensus was reached. Data were extracted directly into tables in Microsoft Word, which were developed, piloted, and modified, as necessary.

For primary studies, detailed information was extracted, including the following:

- description of the publication or source of data (e.g., first author's name, publication year, country where study was conducted, funding source, conflict-of-interest declarations, publication status)
- study characteristics (e.g., primary study objectives, study design, study setting, source of population, inclusion and exclusion criteria [e.g., age, sex, race, type of large B-cell lymphoma], recruitment or sampling procedure, subgroup analyses of interest, statistical analysis methods)
- participant characteristics (e.g., patient disposition [examples include the number of participants enrolled, included in analysis, withdrawn, with missing data, lost to follow-up, number of patients deemed eligible but never received treatment]; demographics and baseline characteristics; type of disease; Eastern Cooperative Oncology Group (ECOG) performance status; r/r status; prior treatment [e.g., chemotherapy or SCT, details of bridging chemotherapy regimen])
- intervention characteristics (e.g., dose)
- outcome characteristics (e.g., definitions of outcomes, measurement method, unit of measurement, length of follow-up)
- results (e.g., measures of clinical effectiveness and safety, number of participants included in the analysis).

For clinical practice guidelines, relevant information was extracted, including:

- target population and intended users
- country of development
- details of the intervention and major outcomes considered
- details of the evidence collection, selection, synthesis, and quality assessment
- methods for developing and evaluating the recommendations
- key recommendations and their level of evidence.

Critical Appraisal of Studies

The critical appraisal of the included studies and guidelines was conducted independently by two reviewers, and consensus was reached through discussion.

The critical appraisal included a global assessment of the study characteristics that contributed to the internal and external validity of the studies. A clinical expert was consulted to assess the generalizability of the eligibility criteria and the baseline patient characteristics to the Canadian clinical context.

Examples of the criteria that were considered in assessing the internal validity of the studies included whether the study was adequately powered, the appropriateness of the statistical analysis (e.g., control of the type I error rate, appropriateness of historical control rate), loss to follow-up, and handling of missing data. Evaluation of the external validity included assessment of whether the participants were representative of the population of interest, the generalizability of the treatment protocol to the Canadian context, and whether the outcomes were considered clinically relevant and important to patients. Other criteria that could affect internal and external validity were also considered.

The quality of included clinical practice guidelines was assessed using the *Appraisal of Guidelines for Research and Evaluation II* instrument.[27]

Data Synthesis

A narrative synthesis was conducted to summarize the findings from the included studies. The relevant data for the narrative synthesis were extracted and summarized in tables with additional description summarized narratively. Results were presented separately for the pivotal trial (ZUMA-1), the indirect treatment comparisons, and the evidence-based guideline. For safety outcomes, the most common AEs or serious adverse events (SAEs), defined as AEs occurring in 10% or more of patients or SAEs occurring in two or more patients were summarized. Notable harms (i.e., cytokine release syndrome [CRS], infections, cytopenias, and neurological events) that occurred in 5% or more of patients were summarized. For ZUMA-1, textual summaries of efficacy and safety focus on the primary analysis and the 24-month analysis, as relevant.

Clinical Review Results

Selection of Included Literature

A total of 749 citations were identified in the literature search. Following screening of titles and abstracts, 694 citations were excluded for various reasons and 55 were retrieved for full-text review. An additional 24 potentially relevant publications were retrieved from other sources (i.e., the manufacturer's submission, grey literature, hand-searching, or search alerts). Of these 79 potentially relevant articles, 41 were excluded for various reasons, and 38 publications met the inclusion criteria and were included in this clinical review.

Of these 38 included reports, 35 contain data from the pivotal trial ZUMA-1 (i.e., three Clinical Study Reports, three full-text articles, and 29 abstracts), two are indirect treatment comparisons submitted by the manufacturer, and one is an eligible evidence-based clinical practice guideline. Of the 41 publications excluded, 16 were described as an ineligible population. Of those publications excluded on the basis of population, 11 conference abstracts described studies of axicabtagene ciloleucel that were distinct from the ZUMA-1 pivotal trial. The eligibility of the study populations described in these 11 abstracts could not be established definitively against the eligibility criteria for this systematic review (see Table 1); specifically, we were not able to ascertain the number of lines of previous therapy used. Consequently, a description of the 11 abstracts was excluded from the main report; however, because these studies did provide insight into the use of axicabtagene ciloleucel in the clinical setting, they have been included in an appendix to the main report (see Appendix 9.

The study selection process is outlined in Appendix 2 using a PRISMA diagram. Lists of included and excluded citations, with details describing the rationale for those excluded, are presented in Appendix 3 and Appendix 4, respectively.

Research Questions #1 and #2:

What are the beneficial effects of axicabtagene ciloleucel for treating adults with eligible types of relapsed or refractory large B-cell lymphoma?

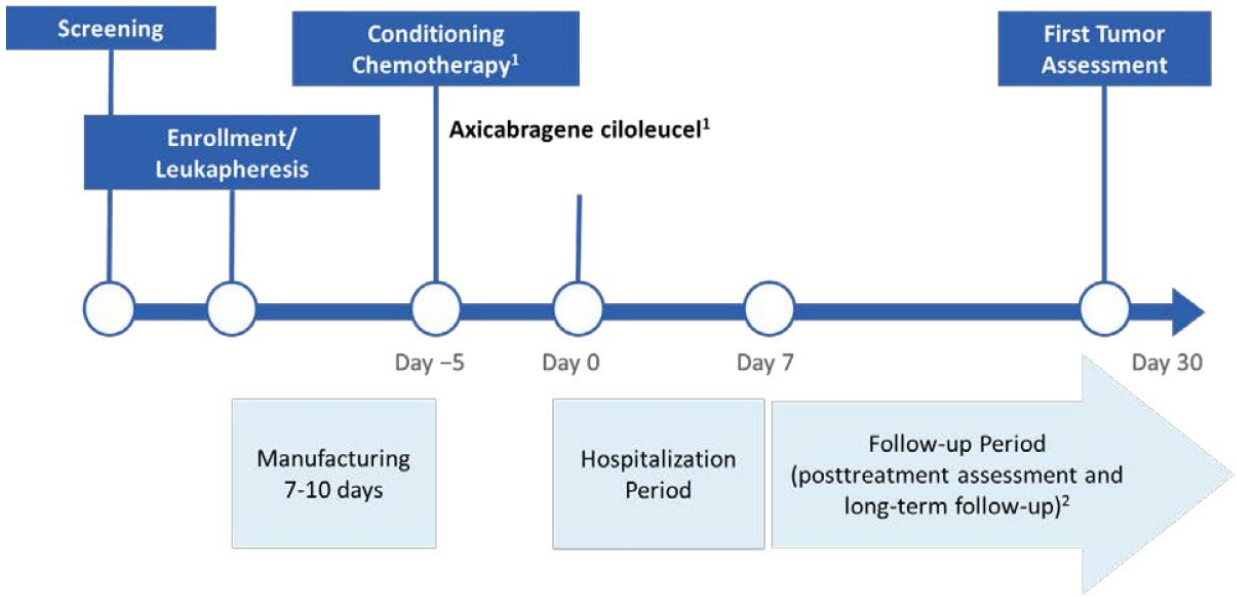
What are the harmful effects of axicabtagene ciloleucel for treating adults with eligible types of relapsed or refractory large B-cell lymphoma?

Study Characteristics of the ZUMA-1 Pivotal Trial

The pivotal trial, ZUMA-1, examined the safety and efficacy of axicabtagene ciloleucel in adults with r/r DLBCL, PMBCL, or transformed follicular lymphoma — namely, DLBCL arising from follicular lymphoma (TFL).[32-34] Information on ZUMA-1 was obtained from the original Clinical Study Report,[32] and 12-[33] and 24-month[34] addenda to the Clinical Study Report, as well as three published reports.[35-37]

ZUMA-1 was a phase I/phase II, single-arm, multi-centre, open-label clinical trial. The overall study design for both phases is illustrated in Figure 2 and a summary of the study characteristics is shown in Table 2 (a complete list of inclusion and exclusion criteria is provided in Appendix 5). The study cohorts and the planned enrolment numbers for phase I and phase II (cohort I and cohort II) are outlined in Figure 3. Phase I has been completed. Phase II is ongoing; enrolment and treatment are complete for cohort I and cohort II, and long-term follow-up is ongoing for patients who remain alive (up to 15 years). A phase II safety management study is still recruiting (this includes cohort III, cohort IV, cohort V, and cohort VI), but is not included in this review, as data for these cohorts were not available.[38] This review reports the findings from phase I, cohort I and cohort II, which were the basis for the submission to Health Canada for regulatory approval. The primary objective of phase I was to evaluate the safety of conditioning chemotherapy and axicabtagene ciloleucel in patients with r/r DLBCL. The primary objective of phase II was to evaluate the efficacy of axicabtagene ciloleucel in patients with r/r DLBCL (cohort I) and PMBCL or TFL (cohort II). ZUMA-1 was conducted at 22 study centres (21 in the US and one in Israel).

Figure 2: Study Design of ZUMA-1



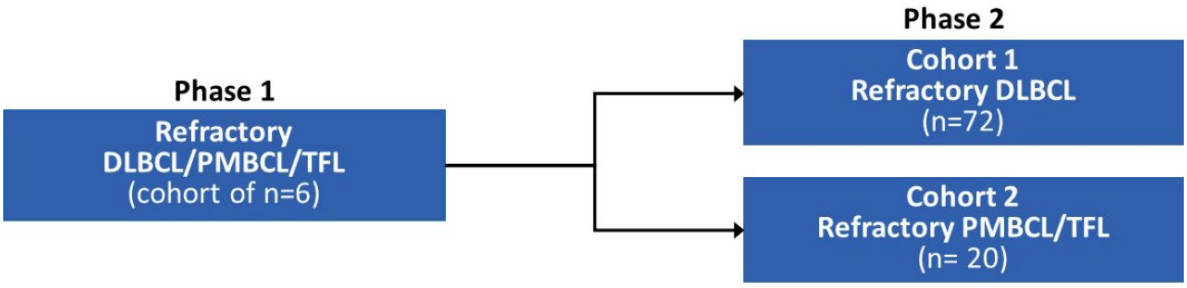
CAR = chimeric antigen receptor.

[a] Axicabtagene ciloleucel treatment consists of conditioning chemotherapy of 500 mg/m^2 cyclophosphamide and 30 mg/m^2 fludarabine on day −5, day −4, and day −3 followed by a target of 2 × 10^6 (± 20%) CAR T cells/kg (minimum 1 × 10^6 CAR T cells/kg) on day 0.

[b] Long-term follow-up for disease status and survival continued every three months through month 18, then every six months through five years, and then annually for a maximum of 15 years.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off).[32]

Figure 3: Study Cohorts and Planned Enrolment



DLBCL = diffuse large B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off).[32]

Table 2: Details of ZUMA-1 Trial Design

		ZUMA-1 (N = 108)
Design and Population	Study design	Phase I/phase II, single-arm, multi-centre, open-label
	Location(s) (country and setting where study was conducted)	**Phase I:** 3 sites in the US **Phase II:** 24 sites (23 in the US and 1 in Israel; medical centres). Two sites recruited 0 patients. Patients were from 22 study centres (21 in the US, 1 in Israel).
	Number of patients infused or treated	**Phase I:** n = 7 **Phase II:** n = 101

	Inclusion criteria	• ≥ 18 years of age
		• Histologically confirmed DLBCL, PMBCL, or TFL according to World Health Organization 2008 criteria
		• Chemotherapy-refractory disease, defined as one of the following:
		  ○ no response to first-line therapy
		  ○ no response to second or greater lines of therapy
		  ○ refractory after autologous SCT (i.e., occurrence of disease progression or relapse ≤ 12 months after autologous SCT)
		• ECOG performance status of 0 or 1
		• Absolute neutrophil count ≥ 1,000/μL
		• Platelet count ≥ 75,000/μL
		• Adequate hematologic, renal, hepatic, pulmonary, and cardiac function
		• Previous treatment with a regimen containing an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen
		• Patients with TFL must have received previous chemotherapy for follicular lymphoma and developed chemo-refractory disease after transformation.

	Exclusion criteria	Patients were excluded if they: • had a requirement for urgent therapy due to tumour mass effects such as bowel obstruction or blood vessel compression • had undergone autologous SCT within 6 weeks of informed consent for ZUMA-1 • had previously undergone allogeneic hematopoietic SCT • had received previous CD19-targeted therapy or CAR T-cell therapy.
Treatments	Intervention	Axicabtagene ciloleucel administered as a single infusion of transduced viable T cells per kg bodyweight at a target dose of 2×10^6 anti-CD19 CAR T cells/kg. Minimum dosage: 1×10^6 anti-CD19 CAR T cells/kg Maximum dosage: 2×10^8 anti-CD19 CAR T cells The following medications were administered 1 hour prior to infusion of axicabtagene ciloleucel: acetaminophen 650 mg oral, diphenhydramine 12.5 mg IV. Patients who achieved a PR or CR had an option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel if their disease subsequently progressed > 3 months following the axicabtagene ciloleucel infusion, provided that the relapse was not known to be $CD19^-$ malignant cells.
	Details of conditioning chemotherapy regimen (prior to axicabtagene ciloleucel infusion)	On day –5, day –4, and day –3 relative to the planned axicabtagene ciloleucel infusion on day 0, conditioning treatment was given as follows: • IV hydration with 1 L of 0.9% sodium chloride (NaCl) • IV cyclophosphamide (500 mg/m2 body surface area) more than 60 minutes • IV fludarabine (30 mg/m2 body surface area) more than 30 minutes • an additional 1 L of 0.9% NaCl • Mesna (sodium 2-mercaptoethanesulfonate) per institutional guidelines.
	Details of bridging therapy	Treatment for lymphoma such as chemotherapy, immunotherapy, targeted agents, radiation, high-dose corticosteroid, and other investigational agents were prohibited between leukapheresis and conditioning chemotherapy in phase I, and in cohort I and cohort II of phase II

		ZUMA-1 (N = 108)
	Comparator(s)	None
Outcomes	Primary end point	**Phase I:** Incidence AEs defined as DLT **Phase II:** ORR (CR + PR) per investigator assessment
	Other end points	**Secondary end points**: • ORR (CR + PR) by IRC • BOR by investigator assessment • BOR by IRC • DOR per investigator assessment • DOR per IRC • PFS per investigator assessment • OS • incidence of AEs, including identified risks (neurological toxicity, CRS, cytopenias [including febrile neutropenia], B-cell aplasia) and potential risks (infections, secondary malignancies) of axicabtagene ciloleucel • incidence and persistence of CAR T cells **Other secondary (exploratory) end points:** • incidence of autologous and allogeneic SCT • incidence and type of anticancer therapy • incidence of concomitant medications used to manage CRS and neurotoxicity
Follow-Up	Definitions of follow-up time	**Actual follow-up time from axicabtagene ciloleucel dose:** Time from the first dose of axicabtagene ciloleucel to date of death or the last date known alive **Potential follow-up time:** Time from axicabtagene ciloleucel infusion to the data cut-off date
	Duration	**Primary analysis:** Followed the first 72 patients in cohort I and the first 20 patients in cohort II of the modified intention-to-treat analysis set when all patients had the opportunity to be followed for at least 6 months (follow-up through January 27, 2017) **12-month addendum:** Conducted an updated analysis for phase II, cohort I (DLBCL) and cohort II (PMBCL and TFL) for all 101 treated patients when all patients had the opportunity to be followed for 12 months (follow-up through August 11, 2017) **24-month addendum:** Conducted an updated analysis for phase II, cohort I and cohort II for all 101 treated subjects when all patients had the opportunity to be followed for a minimum of 24 months or until death (follow-up through 11 August 2018)
Published and Unpublished Reports	Primary analysis (6-month analysis)	Main CSR;[32] Neelapu et al. (2017)[35]
	12-month analysis	12-month CSR addendum;[33] Neelapu et al. (2017)[35]
	24-month analysis	24-month CSR addendum;[34] Locke et al. (2019)[37]
	Abstracts	29 ZUMA-1 conference abstracts (Appendix 3)[39-67]

AE = adverse event; BOR = best objective response; CAR = chimeric antigen receptor; CR = complete response or complete remission; CRS = cytokine release syndrome; CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; IRC = Independent Central Review Committee; IV = intravenous; NaCl = sodium chloride; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response or partial remission; r/r = relapsed or refractory; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

Source: Information submitted by manufacturer (CSR, January 27, 2017, data cut-off; CSR, August 11, 2017; CSR, August 11, 2018, data cut-off),[32-34] Neelapu et al. 2017,[35] and Locke et al. 2019.[37]

Population

Patients were eligible for inclusion in ZUMA-1 if they had histologically confirmed r/r large B-cell lymphoma (DLBCL, PMBCL, or TFL). Complete inclusion and exclusion criteria are presented in Appendix 5. At baseline, the median age of all phase II patients in the ZUMA-1 trial (cohort I and cohort II combined) was 58.0 years (range 23 to 76), and the majority were white 89%) and male (67%). Patients included 77 (76%) with DLBCL, eight (8%) with PMBCL, and 16 (16%) with TFL. Most patients had stage III or IV lymphoma (85%), and had an ECOG performance status score of zero (42%) or one (58%). The majority of patients were refractory to second-line or subsequent therapy (77%); others had relapsed after autologous SCT (21%) or had primary refractory disease (2%). Additional information on patient characteristics is reported in Table 3.

Table 3: Baseline Characteristics

	Primary Analysis			
	Phase I	**Cohort I (DLBCL)**	**Cohort II (PMBCL, TFL)**	**Cohort I and Cohort II (DLBCL, PMBCL, TFL)**
Sample size (primary analysis set), n	7	77	24	101
Age, years, mean (standard deviation)	52.4 (17.5)	57.4 (10.6)	53.0 (15.5)	56.3 (12.0)
Age, years, median (range)	59.0 (29 to 69)	58.0 (25 to 76)	57.0 (23 to 76)	58.0 (23 to 76)
Age, ≥ 65, n (%)	3 (43)	17 (22)	7 (29)	24 (24)
Sex				
Male, n (%)	5 (71)	50 (65)	18 (75)	68 (67)
Female, n (%)	2 (29)	27 (35)	6 (25)	33 (33)
Weight				
Kg, mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Kg, median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)				
White	6 (86)	71 (92)	19 (79)	90 (89)
Asian	0 (0)	1 (1)	3 (13)	4 (4)
Black or African American	1 (14)	3 (4)	1 (4)	4 (4)
Other	0 (0)	2 (3)	1 (4)	3 (3)
Country, n (%)				
US	7 (100)	77 (100)	23 (96)	100 (99)
Israel	0 (0)	0 (0)	1 (4)	1 (1)
Stage (At Study Entry), n (%)				
Stage I or II	3 (43)	10 (13)	5 (21)	15 (15)
Stage III or IV (advanced)	4 (57)	67 (87)	19 (79)	86 (85)
IPI (At Study Entry), n (%)				
< 2	3 (43)	16 (21)	11 (46)	27 (27)
≥ 2	4 (57)	61 (79)	13 (54)	74 (73)
Disease Type, local, n (%)				

	Primary Analysis			
	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
DLBCL	7 (100)	77 (100)	0 (0)	77 (76)
PMBCL	0 (0)	0 (0)	8 (33)	8 (8)
TFL	0 (0)	0 (0)	16 (67)	16 (16)
Disease Subtype, n (%)				
DLBCL not otherwise specified	7 (100)	75 (97)	0 (0)	75 (74)
DLBCL associated with chronic inflammation	0 (0)	1 (1)	0 (0)	1 (1)
PMBCL	0 (0)	0 (0)	8 (33)	8 (8)
TFL	0 (0)	0 (0)	16 (67)	16 (16)
Other (unspecified)	0 (0)	1 (1)	0 (0)	1 (1)
CD19 Status,[a] n (%)				
Negative	2 (29)	7 (9)	1 (4)	8 (8)
Positive	3 (43)	56 (73)	18 (75)	74 (73)
Missing	2 (29)	14 (18)	5 (21)	19 (19)
ECOG Performance Status				
Score of 0, n (%)	4 (57)	28 (36)	14 (58)	42 (42)
Score of 1, n (%)	3 (43)	49 (64)	10 (42)	59 (58)
Number of Previous Chemotherapy Regimens, n (%)				
1	0 (0)	2 (3)	0 (0)	2 (2)
2	1 (14)	26 (34)	3 (13)	29 (29)
3	5 (71)	22 (29)	8 (33)	30 (30)
4	1 (14)	20 (26)	8 (33)	28 (28)
5	0 (0)	4 (5)	2 (8)	6 (6)
> 5	0 (0)	3 (4)	3 (13)	6 (6)
Autologous SCT				
Patients with prior autologous SCT, n (%)	4 (57)	18 (23)	7 (29)	25 (25)
Relapse/Refractory Subgroup at Study Entry, n (%)				
Primary refractory	0 (0)	2 (3)	0 (0)	2 (2)
Refractory to second-line or subsequent therapy	3 (43)	59 (77)	19 (79)	78 (77)
Relapse after autologous SCT	4 (57)	16 (21)	5 (21)	21 (21)
Response to Last Chemotherapy Regimen (For Those Not Relapsed After Autologous SCT), n (%)				
Stable disease	0 (0)	10 (13)	4 (17)	14 (14)
Progressive disease	3 (43)	51 (66)	15 (63)	66 (65)
Presence of B Symptoms, n (%)				
Yes	1 (14)	7 (9)	2 (8)	9 (9)
No	6 (86)	70 (91)	22 (92)	92 (91)
Bulky Disease, n (%)				
Yes	0 (0)	14 (18)	3 (13)	17 (17)
No	7 (100)	63 (82)	21 (88)	84 (83)
Extranodal Disease, n (%)				
Yes	3 (43)	54 (70)	16 (67)	70 (69)

	Primary Analysis			
	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
No	4 (57)	23 (30)	8 (33)	31 (31)

DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; PMBCL = primary mediastinal large B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

[a] Not all patients had an evaluable sample for CD19 status. In phase I , 5 patients were evaluable for CD19, and in phase II, 82 patients were evaluable.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off),[32] European Medicines Agency,[18] and FDA.[68]

Intervention

T cells were collected from patients by leukapheresis according to local requirements [redacted].

In cohort I and cohort II of ZUMA-1, bridging therapy (i.e., chemotherapy, immunotherapy, targeted agents, radiation, high-dose corticosteroid, and other investigational agents) was not permitted between leukapheresis and the administration of axicabtagene ciloleucel. Patients were treated with lymphodepleting chemotherapy (i.e., "conditioning chemotherapy") prior to infusion of axicabtagene ciloleucel. Conditioning chemotherapy consisted of fludarabine (30 mg/m^2 body surface per day) and cyclophosphamide (500 mg/m^2 body surface per day) on day 5, day 4, and day 3 prior to the planned axicabtagene ciloleucel infusion on day 0 (complete details in Table 2 and Table 10). Axicabtagene ciloleucel was administered as a single infusion of transduced viable T cells per kg body weight at a target dose of 2 × 10^6 anti-CD19 CAR T cells/kg. The minimum dose to be administered was 1 × 10^6 anti-CD19 CAR T cells/kg, and the maximum dose was 2 × 10^8 anti-CD19 CAR T cells. Almost all patients received the target dose; [redacted] Patients who had an initial response and then had disease progression at least three months after the first dose of axicabtagene ciloleucel could be re-treated. Details on dose administration for both conditioning chemotherapy and axicabtagene ciloleucel are presented in Table 10.

Outcomes

Outcomes were assessed according to the following schedule: disease assessments for efficacy outcomes (e.g., for assessment of ORR) took place at four weeks, every three months until month 18, and at month 24. After two years, disease assessment took place every six months, until six years, and then annually. Patients will continue to be followed for 15 years. Assessments of disease were completed by study investigators (investigator assessment) and by an independent central review committee (IRC) according to the International Working Group (IWG) revised response criteria for malignant lymphoma.[69] The terms "response" and "remission" may be used interchangeably.

Starting at six months, survival status assessment followed the same schedule as the disease assessments. Blood draws for anti-CD19 CAR+ T cells were scheduled for week 1, week 2, and week 4, and month 3, month 6, month 12, and month 24. Targeted concomitant medications followed the same schedule of assessments as survival status, and were collected until two years after disease progression. Subsequent therapy for large B-cell lymphoma administered after axicabtagene ciloleucel followed the same schedule of assessments as survival status. With the exception of OS, efficacy outcomes to *re-treatment* with axicabtagene ciloleucel were determined separately in the subset of patients who underwent re-treatment with axicabtagene ciloleucel.

Efficacy Outcomes

Overall Response Rate

In phase II of ZUMA-1, the primary outcome was the investigator assessment of ORR, defined as the proportion of patients with either a complete response (CR; disappearance of all evidence of disease) or partial response (PR; regression of measurable disease and no new sites) *at any time* while on study (see Table 4).

Secondary response rate outcomes included ORR assessed by IRC and best objective response (per the investigator assessment, and by IRC), as defined in Table 4.

Time-to-Event Analyses

Secondary time-to-event end points in ZUMA-1 were duration of response (DOR) (per the investigator assessment, and by IRC), progression-free survival (PFS) (per the investigator assessment), and OS, as defined in Table 4.

Other Secondary Outcomes

Additional exploratory outcomes in ZUMA-1 included the incidence of autologous and allogeneic SCT, the incidence and type of subsequent anticancer therapy, and the use of concomitant medications, as defined in Table 4.

Table 4: Efficacy Outcome Characteristics for ZUMA-1

Outcomes and Characteristics	Details
Primary Outcome	
(ORR) by Investigator Assessment	
Definition	The proportion of patients with either a CR (i.e., disappearance of all evidence of disease) or PR (i.e., regression of measurable disease and no new sites) at any time while on study See Appendix 6 (Table 32) for definitions of CR and PR.
Method of assessment	Assessed by the study investigators according to the IWG revised response criteria for malignant lymphoma[69]
Length of follow-up	Primary analysis occurred when 92 patients (72 in cohort I and 20 in cohort II) had the opportunity to be followed for at least 6 months
Secondary Outcomes	
ORR by IRC	
Definition	The proportion of patients with either a CR or PR at any time while on study
Method of assessment	Assessed by an IRC according to the IWG revised response criteria for malignant lymphoma[69]
Duration of Response	
Definition	The time from the first objective response to disease progression or death due to disease relapse or drug-related toxicity; measured only for patients who experienced an objective response
Method of assessment	Calculated based on patient assessment dates reported by investigator and disease assessments by the study investigators or IRC
Best Overall Response	
Definition	The most favourable assessment of response (CR, PR, SD, PD, not evaluable, and not done) for each patient at each time point using IWG 2007 criteria[69] See Appendix 6 (Table 32) for definitions of CR, PR, SD, and PD
Progression Free Survival	
Definition	The time from the axicabtagene ciloleucel infusion date to the date of disease progression or death from any cause
Method of assessment	Calculated based on patient assessment dates reported by investigator and disease assessments by the study investigators or IRC
Overall Survival	
Definition	The time from axicabtagene ciloleucel infusion to the date of death from any cause
Method of assessment	The last date known to be alive was derived by obtaining the maximum complete date from following data modules: • start date of AE (including targeted AE) • leukapheresis dates • conditioning chemotherapy administration dates • axicabtagene ciloleucel infusion dates • CT scan dates • positron emission tomography scan dates • clinical symptoms of lymphoma assessment dates • target lesion assessment • non-target lesion assessment • new lesion assessment • disease response assessment • long-term follow-up patient status date where status = “alive” • end-of-treatment disposition where status is not equal to death, lost to follow-up

Outcomes and Characteristics	Details
	• end-of-post–treatment assessment period where status is not equal to death, lost to follow-up • end-of-study data where end-of-study reason is not equal to death, lost to follow-up
Persistence and Levels of Anti-CD19 CAR T Cells	
Definition	Continued presence (detectable) and concentration of anti-CD19 CAR T cells in the blood
Method of assessment	Quantitative polymerase chain reaction analysis
Subsequent Anti-Cancer Therapy	
Definition	Incidence and type (by World Health Organization drug-coded term and categories) of subsequent anticancer therapy and stem cell transplant (autologous or allogeneic stem cell transplant)
Duration of Hospitalization for Axicabtagene Ciloleucel Infusion	
Definition	Period during which the patient remained in hospital for the axicabtagene ciloleucel infusion

AE = adverse event; CAR = chimeric antigen receptor; CR = complete response; IRC = Independent Central Review Committee; IWG = International Working Group; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off; Study Protocol, August 12, 2016, amendment)[32] and Locke et al. 2019.[37]

Safety Outcomes

For safety outcomes, all AEs and SAEs observed by the investigator or reported by the patient from enrolment (i.e., commencement of leukapheresis) through three months following axicabtagene ciloleucel infusion were monitored and reported. After three months, targeted AEs or severe AEs (e.g., neurologic events, hematologic events, infections, autoimmune disorders, and secondary malignancies) were collected for 24 months after treatment or until disease progression, whichever occurred first. AEs were graded according to the National Cancer Institute's *Common Terminology Criteria for Adverse Events (CTCAE) v4.03*. For patients who were enrolled but did not receive axicabtagene ciloleucel, the AE reporting period ended 30 days after the last study-specific procedure (e.g., leukapheresis, conditioning chemotherapy).

SAEs were collected from screening. After month 3 and until 24 months or disease progression, whichever occurred first, only the following targeted SAEs were collected: neurologic events, hematologic events, infections, autoimmune disorders, and secondary malignancies. For patients who screen-failed or were enrolled but did not receive axicabtagene ciloleucel, the reporting period for SAEs ended 30 days after the last procedure (e.g., screen procedure, leukapheresis, conditioning chemotherapy).

Characteristics of safety outcomes are presented in Table 5. Characteristics of the notable harms, as defined in ZUMA-1, are presented in Appendix 6.

Table 5: Safety Outcome Characteristics for ZUMA-1

	Details
AE	
Definition	• This is any untoward medical occurrence in a clinical trial patient, irrespective of whether the event was related to the study treatment, including worsening of a pre-existing medical condition (i.e., increased severity, frequency, and/or duration of pre-existing condition, or association between a pre-existing condition and a worse outcome). • A pre-existing condition that did not worsen during the study, or involved an intervention such as elective cosmetic surgery or a medical procedure while on study, was not considered an AE. • Treatment-emergent AEs were defined as any AE that occurred after the start of conditioning chemotherapy.
SAE	
Definition	This is an AE that met at least 1 of the following serious criteria: • was fatal • was life threatening (placed the patient at immediate risk of death) • required in-patient hospitalization (i.e., necessitated admission) or prolongation of existing hospitalization (e.g., overnight stay) • resulted in persistent or significant disability/incapacity • was a congenital anomaly/birth defect • was another medically important serious event. Events that required an escalation of care when the patient was already hospitalized (e.g., movement from routine care in the hospital to the intensive care unit, or prolongation of the existing planned hospitalization) were recorded as a SAE.

AE = adverse event; SAE = serious adverse event.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off; Study Protocol, August 12, 2016, amendment),[32] and Locke et al. 2019.[37]

Statistical Analysis for ZUMA-1

Five analyses of the data from ZUMA-1 had been performed at the time of this systematic review:

- interim analysis 1, when 20 patients in the modified intention-to-treat (mITT) set of cohort I had the opportunity to be evaluated for response three months after axicabtagene ciloleucel infusion (data cut-off: June 16, 2016)
- interim analysis 2, when 50 patients in the mITT cohort I had the opportunity to be evaluated for response three months after axicabtagene ciloleucel infusion (data cut-off: August 24, 2016)
- primary analysis, when the first 92 patients had the opportunity to be followed for at least 6 months after axicabtagene ciloleucel infusion (data cut-off: January 27, 2017)
- 12-month analysis (data cut-off: August 11, 2017)[35]
- 24-month analysis, when the surviving patients from the mITT had been followed for at least 24 months (data cut-off: August 11, 2018).[35]

The statistical analysis approach used by the study investigators is described as follows.

Power Calculation

The anticipated enrolment in phase I and phase II of ZUMA-1 was approximately 98 to 116 patients. Planned enrolment in phase I was between six to 24 patients, and in phase II, approximately 72 and 20 patients were to be enrolled in cohort I (DLBCL) and cohort II (PMBCL, TFL), respectively.

No sample size or power calculations were provided for ZUMA-1; however, the following sample size considerations were reported.[32] Phase II of the ZUMA-1 study was designed to inferentially test for an improvement in ORR in cohort I (DLBCL; approximately n = 72) and in cohort I and cohort II combined (n = 92), relative to a historical control rate. It was hypothesized that the ORR to axicabtagene ciloleucel in phase II would be statistically significantly greater than 20%. With 92 patients enrolled in phase II, ZUMA-1 would have 90% or more power to distinguish between an active therapy with a 40% true response rate from a therapy with a response rate of 20% or less with a one-sided alpha of 0.025, divided between the inference for cohort I (0.022) and the inference for cohort I and cohort II combined (0.0075).

Statistical Method

Interim Analyses

ZUMA-1 included two preplanned interim analyses prior to the analysis of the primary end point. The first interim analysis of ZUMA-1 was performed when 20 patients in the mITT set of cohort I had the opportunity to be evaluated for response three months after axicabtagene ciloleucel infusion (data cut-off: June 16, 2016). The purpose of this analysis was to assess futility. Given that the futility criterion was not met, ZUMA-1 continued as planned.

The purpose of the second interim analysis was to assess early demonstration of efficacy and was conducted when 50 patients in the mITT of cohort I had the opportunity to be evaluated for response three months after axicabtagene ciloleucel infusion (data cut-off: August 24, 2016). While the criteria for early efficacy were met at the second interim analysis, the sponsor of ZUMA-1 chose to complete the trial because the enrolment of patients in cohort I and cohort II was near completion.

Primary End Point

The primary end point of ZUMA-1 was the investigator assessment of ORR analyzed in cohort I and cohort II combined when 72 patients in cohort I and 20 patients in cohort II in the mITT set (defined in the Analysis Population section) had the opportunity to be followed for at least six months following axicabtagene ciloleucel infusion (total sample size of 92 for the analysis of the primary end point). A one-sided exact binomial test was used to compare the ORR to the hypothesized historical control rate of 20%. The threshold of 20% was based on a review of the limited literature available in which responses to salvage therapy ranged from 0% to 26% in patients with NHL who were refractory to first-line therapy or second-line therapy or relapsed following autologous SCT. To provide a more rigorous assessment of response to salvage chemotherapy among patients with chemo-refractory disease, a retrospective review of patient outcome data from four institutions was conducted, referred to as SCHOLAR-1 (see Appendix 10). The results from SCHOLAR-1 indicated a response rate of 26% among 523 refractory DLBCL patients. The statistical testing of the primary end point in cohort I and cohort II was performed at a one-sided alpha level of 0.0075. This was to adjust for a preplanned analysis of investigator-assessed ORR in cohort I alone at a one-sided alpha level of 0.0220. However, given that the primary end point for the analysis of cohort I was met at the second interim analysis, the preplanned analysis of cohort I for the primary end point was not performed.

The ORR for the primary analysis of cohort I and cohort II combined was presented as the percentage of patients who achieved CR or PR, along with a two-sided 95% exact Clopper–Pearson confidence interval (CI). Sensitivity analyses were conducted to calculate the CI

using three different methods (Wilson's method, the Agresti–Coull method, and the modified Jeffreys method).

All patients who did not meet the criteria for objective response by the data analysis cut-off date were considered non-responders. The primary mITT analysis of ORR included only response assessments obtained after the initial axicabtagene ciloleucel infusion and prior to any other additional therapy. For the outcome ORR, disease assessments obtained after re-treatment with axicabtagene ciloleucel were excluded.

Secondary End Points

Secondary efficacy end points were presented descriptively at the primary analysis, and at the 12-month and 24-month cut-offs. Details are provided in Table 6.

The investigator-assessed ORR and corresponding 95% CIs were also presented descriptively for the complete mITT set, which included a total of 101 patients (77 in cohort I and 24 in cohort II); however, no inferential testing was planned for the complete mITT set. Analyses of the ORR in the mITT set were performed at the time of the primary analysis and the 12-month addendum (data cut-off: August 11, 2017)[35] and in the 24-month analysis of ZUMA-1 (August 11, 2018),[37] when the surviving patients had been followed for at least 24 months. However, it was specified that no inferential testing was to be performed at the longer data cut-offs.

Table 6: Statistical Analysis of Secondary Efficacy End Points

End Point	Disease Assessment	Unit of Measurement and Statistical Model	Other Details
Measures of Response			
ORR	Investigator assessment IRC	Percentage of patients who achieved CR or PR, along with a 2-sided, 95% exact Clopper–Pearson CI. Repeated statistical analysis of ORR by the investigator assessment but without control of the type I error rate.	• The concordance of ORR assessed by the investigator and by IRC was evaluated using concordance, concordance rate, a kappa statistic, and a 2-sided, 95% CI about the kappa statistic.
Best overall response	Investigator assessment IRC	Percentage of patients with best response (CR, PR, stable disease, progressive disease, not evaluable, or not done) was reported, and 95% Clopper–Pearson CIs were calculated at the 24-month analysis.	
Time-to-Event End Points			
DOR	Investigator assessment IRC	Months; KM estimates of the probability of being in response at a given time point Cumulative incidence functions, KM curves, and median time to event	• Patients not meeting the criteria for progression or death due to disease relapse or drug-related toxicity by the analysis data cut-off date were censored at their last evaluable disease assessment date. • The number of patients censored and the reasons for censoring were summarized. Mortality not related to disease was considered a competing risk. • In the event that patients had a competing risk event, DOR was calculated as the time

End Point	Disease Assessment	Unit of Measurement and Statistical Model	Other Details
			from the first objective response to the time of the competing risk event. • DOR was derived using disease assessments obtained on study prior to initiation of new anticancer therapy or re-treatment with axicabtagene ciloleucel. • Assessments following [redacted] were included in the derivation of DOR, [redacted]
PFS	Investigator assessment	Months; KM estimates of the probability of having PFS at a given time point Cumulative incidence functions, KM curves, and median time to event	• Disease assessments were obtained on study prior to initiation of new anticancer therapy or re-treatment with axicabtagene ciloleucel. Assessments following autologous SCT were included in the derivation of PFS. • The number of patients censored and the reasons for censoring were summarized. • Patients not meeting the criteria for progression by the analysis data cut-off date (i.e., response ongoing) were censored at their last evaluable disease assessment date. • Assessments following autologous or [redacted] were included in the derivation of PFS, [redacted]
OS		Months Cumulative incidence functions, KM curves, and median time to event	• Patients who had not died by the analysis data cut-off date were censored at their last date known to be alive prior to the data cut-off date, with the exception that patients known to be alive or determined to have died after the data cut-off date for the analysis were censored at the data cut-off date. [redacted]
Exploratory End Points			
Subsequent autologous and allogeneic SCT	Investigator assessment IRC	[redacted]	
Subsequent anticancer therapy	Investigator assessment	[redacted]	
Concomitant medications used to manage CRS and neurotoxicity	NA	[redacted]	
Safety			

End Point	Disease Assessment	Unit of Measurement and Statistical Model	Other Details
AEs	NA	Number and percentage of patients experiencing AEs	If a patient began a new anticancer therapy, the AE reporting period for non-serious AEs ended at the time the new treatment was started. Includes identified risks (neurological toxicity, CRS, cytopenias [including febrile neutropenia], B-cell aplasia) and potential risks (infections, secondary malignancies) of axicabtagene ciloleucel
Persistence of CAR T cells	NA	Number of CAR-positive viable T cells per microlitre of blood	Measured at baseline (prior to conditioning chemotherapy), and at day 7, week 2, week 4, month 3, and later time points for patients with available samples

AE = adverse event; CAR = chimeric antigen receptor; CI = confidence interval; CR = complete response; CRS = cytokine release syndrome; DOR = duration of response; IRC = Independent Central Review Committee; KM = Kaplan–Meier; NA = not applicable; ORR = objective response rate; PFS = progression-free survival; PR = partial response; SCT = stem cell transplant.

Source: Information submitted by manufacturer (Statistical Analysis Plan, August 28, 2016, amendment) and Locke et al. 2019.[37]

Handling Missing Data and Censoring

Partial or missing dates were imputed using an algorithm for the following: AE start dates, concomitant medication start dates, subsequent anticancer therapy start dates, and death. For time-to-event end points (e.g., DOR, PFS, OS), a priori decision rules were used to determine the date of events and censoring.

The censoring rules for the time-to-event end points in ZUMA-1 were according to the following:[37]

- **DOR:**
  - At the primary analysis, patients not meeting the criteria for disease progression, or disease- or treatment-related death, were censored for ongoing response or the start of new anticancer therapy (*excluding* allogeneic SCT while in response) at their last evaluable disease assessment date.
  - At the 24-month analysis, patients not meeting the criteria for disease progression, or disease- or treatment-related death, were censored for ongoing response, [redacted]
- **PFS:**
  - At the primary analysis, patients not meeting the criteria for disease progression, or disease- or treatment-related death, were censored for ongoing response, the start of new anticancer therapy (*excluding* allogeneic SCT while in response), or response not yet assessed.
  - At the 24-month analysis, patients not meeting the criteria for disease progression, or disease- or treatment-related death, were censored for ongoing response, [redacted]
- **OS:** Patients who had not died by the data cut-off date were censored at their last date known to be alive prior to the data cut-off date. Patients known to be alive or determined

to have died after the data cut-off date were censored at the data cut-off date. All patient follow-up (including any after re-treatment with axicabtagene ciloleucel) was included in OS.

For patients who were re-treated with axicabtagene ciloleucel, disease assessments obtained prior to re-treatment but not after re-treatment were included in the analyses of ORR, DOR, and PFS. Additional details regarding efficacy outcome definitions and censoring rules are provided in Table 4.

Subgroup Analyses

In ZUMA-1, a number of patient characteristics were pre-specified in the statistical analysis plan as potential subgroup analyses and are outlined as follows. Those that were pre-specified as subgroups of interest in our protocol for this systematic review are bolded:[23]

- **age (younger than 65, and 65 and older)**
- **ECOG performance status (score of zero or one)**
- International Prognostic Index risk score (zero to two, and three to four)
- **number of prior chemotherapies**
- **type of lymphoma (DLBCL, PMBCL, TFL)**
- **cell of origin**
- **relapse/refractory status**
- **refractory to first-line therapy**
- **refractory to two or more lines of therapy**
- **tumour burden**
- history of bone marrow involvement
- **stage of disease (I to II, and III to IV)**
- extranodal disease
- bulky disease
- presence of B symptoms
- **double expressor and high-grade B-cell lymphoma (BCL2, BCL6, C-MYC**)
- **sex**
- **race (white, Asian, and other)**
- **histological score (CD19**)
- CD4/CD8 ratio
- steroid use
- tocilizumab use
- glucocorticoid use
- splenic involvement

Sensitivity Analyses

A sensitivity analysis of ORR by the investigator assessment was conducted in the full analysis set at the primary analysis [redacted] In the mITT analysis set, the concordance of ORR by the investigator assessment and by IRC was evaluated using overall concordance and a kappa coefficient with a two-sided 95% CI.

A sensitivity analysis of OS was conducted in the full analysis set of all enrolled patients (i.e., including patients who underwent leukapheresis but did not receive an infusion of axicabtagene ciloleucel). A sensitivity analysis of DOR by the investigator assessment was conducted in the full analysis set at the primary analysis and at the 24-month analysis (not described in this report).

Analysis Populations

The analysis sets in ZUMA-1 are provided in Table 7. The primary efficacy analysis of phase I was performed using the safety analysis set while the primary efficacy analysis of phase II used the mITT set. Primary analyses of the safety outcomes for both phase I and phase II were performed using the safety analysis set. Sensitivity analyses for ORR, OS, and DOR were performed in the full analysis set, which included all enrolled patients (i.e., patients who underwent leukapheresis but did not receive an infusion of axicabtagene ciloleucel).

Table 7: Analysis Sets in ZUMA-1

Analysis Set	Phase I, n (%)	Cohort I (DLBCL), n (%)	Cohort II (PMBCL, TFL), n (%)	Cohort I and Cohort II (DLBCL, PMBCL, TFL), n (%)	Definition
Full analysis set	8 (100)	81 (100)	30 (100)	111 (100)	• All enrolled patients • To be used for summary of patient disposition, sensitivity analyses of ORR, OS, and DOR, and patient listings of death
mITT (phase II only)	NA	77 (95)	24 (80)	101 (91)	• All patients treated with at least 1.0 x 10^6 anti-CD19 CAR T cells/kg in phase II • Used for all efficacy analyses in phase II
Safety analysis set[a]	7 (88)	77 (95)	24 (80)	101 (91)	• All patients treated with any dose of axicabtagene ciloleucel • For the primary analysis, all treated patients were included, regardless of follow-up time.
DLT-evaluable set (phase I only)	6 (75)	NA	NA	NA	• Patients treated in phase I who either: (1) received the target number of cells (2.0 [± 20%] x 10^6 anti-CD19 CAR T cells/kg) and were followed for at least 30 days after axicabtagene ciloleucel infusion, or (2) received a cell dose lower than the target but experienced a DLT during the 30 days post-infusion
Re-treatment mITT analysis set	NA	8 (10)	1 (3)	9 (8)	[redacted]

Analysis Set	Phase I, n (%)	Cohort I (DLBCL), n (%)	Cohort II (PMBCL, TFL), n (%)	Cohort I and Cohort II (DLBCL, PMBCL, TFL), n (%)	Definition
Re-treatment safety analysis set	1 (13)	8 (10)	1 (3)	9 (8)	[redacted]

DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicities; mITT = modified intention-to-treat; NA = not applicable; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

[a] In phase II, the safety analysis set includes the same patients as the mITT, as all patients received the necessary dosage for the mITT analysis.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off),[32] European Medicines Agency,[18] and FDA.[68]

Patient Disposition

Patient disposition is summarized in Table 8. In phase I, 11 patients were screened and eight were enrolled; the reasons for not enrolling the other three patients were not reported. Of the eight patients, all underwent leukapheresis, but one was discontinued prior to conditioning chemotherapy due to [redacted] disease progression. Therefore, seven patients were treated with conditioning chemotherapy and infused with axicabtagene ciloleucel.

In phase II, 124 patients were screened and 111 were enrolled. Thirteen patients were screened but not enrolled for the following reasons (based on ZUMA-1 eligibility criteria):

[redacted]

All of the 111 enrolled patients underwent leukapheresis, 103 were treated with conditioning chemotherapy, and 101 were infused with axicabtagene ciloleucel. Of the 10 patients who were enrolled but did not receive axicabtagene ciloleucel infusion, five had an AE, [redacted] died, and two had non-measurable disease before conditioning chemotherapy.

Overall, seven patients were infused with axicabtagene ciloleucel in phase I, and 101 patients infused in phase II, for a total of 108 patients. The analysis sets are described in Table 7. Unless otherwise specified, data are presented for patients who were infused with axicabtagene ciloleucel (i.e., the safety analysis data set for phase I and the mITT data set for phase II).

Table 8: Patient Disposition

	Primary Analysis Through 24-Month Analysis			
	Phase I	**Cohort I (DLBCL)**	**Cohort II (PMBCL, TFL)**	**Cohort I and Cohort II (DLBCL, PMBCL, TFL)**
Screened, N	11	NR	NR	124
Not enrolled, n	3	NR	NR	13
Enrolled, n	8	81	30	111
Discontinued Before infusion, n (%)				
Overall	1 (13)	4 (5)	6 (20)	10 (9)
Adverse event	1 (13)	3 (4)	2 (7)	5 (5)
Death	0 (0)	1 (1)	2 (7)	[redacted]
Non-measurable disease	0 (0)	0 (0)	2 (7)	2 (2)
Axicabtagene Ciloleucel-Infused Patients, n (%)				
Overall	7 (88)	77 (95)	24 (80)	101 (91)
Primary Reason for Ending Study in Patients Treated With Axicabtagene Ciloleucel				
January 27, 2017, data cut-off (primary analysis)				
Death	4 (50)	[redacted]	[redacted]	[redacted]
August 11, 2018, data cut-off (24-month analysis)				
Death	4 (50)	[redacted]	[redacted]	[redacted]
Analyses Sets				
Full analysis set	8 (100)	81 (100)	30 (100)	111 (100)
mITT	NA	77 (95)	24 (80)	101 (91)
Safety analysis set	7 (88)	77 (95)	24 (80)	101 (91)

CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; mITT = modified intention-to-treat; NA = not applicable; NR = not reported; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off).[32] For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off),[34] Locke et al. 2019,[37] and FDA.[68]

Exposure to Study Treatments

Study Treatments

The exposure to axicabtagene ciloleucel is summarized in Table 9. There were 11 patients who were leukapheresed but did not receive an infusion of axicabtagene ciloleucel. Two of these 11 patients were treated with conditioning chemotherapy but did not receive an infusion of axicabtagene ciloleucel. Almost all patients received the target dose of axicabtagene ciloleucel; in phase I, one patient (14%) received less than the minimum target dose, and one patient (14%) received compromised doses. In phase II, three patients (3%) received compromised doses (see footnote in Table 10). Patients who had an initial response and then had disease progression at least three months after the first dose of axicabtagene ciloleucel could be re-treated. Details on axicabtagene ciloleucel dose and administration are presented in Table 10.

Table 9: Study Treatments

	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Leukapheresed patients, n (%)	8 (100)	81 (100)	30 (100)	111 (100)
Patients treated with conditioning chemotherapy, n (%)	7 (88)	77 (95)	26 (87)	103 (93)
Discontinued before infusion, n (%)	1 (13)	4 (5)	6 (20)	10 (9)
Axicabtagene ciloleucel-infused patients, n (%)	7 (88)	77 (95)	24 (80)	101 (91)
Summary of Study Treatment Days				
Days from leukapheresis to commencement of conditional chemotherapy, median (range)	17 (12 to 37)	17 (10 to 62)	18 (13 to 64)	17 (10 to 64)
Days from leukapheresis to administration of axicabtagene ciloleucel, median (range)	22 (17 to 42)	23 (15 to 72)	23 (18 to 69)	23 (15 to 72)
Days from conditioning chemotherapy to administration of axicabtagene ciloleucel, median (range)	5 (5 to 5)	5 (5 to 12)	5 (5 to 6)	5 (5 to 12)
Days from leukapheresis to delivery of axicabtagene ciloleucel at study site, median (range)	16 (14 to 23)	17 (14 to 44)	17 (14 to 51)	17 (14 to 51)

DLBCL = diffuse large B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off).[32]

Table 10: Axicabtagene Ciloleucel Dose Administration

	Primary Analysis			
	Phase I (N = 7)	Cohort I (DLBCL) (N = 77)	Cohort II (PMBCL, TFL) (N = 24)	Cohort I and Cohort II (DLBCL, PMBCL, TFL) (N = 101)
Total Axicabtagene Ciloleucel Dose Infused (x 10^6 CAR-Positive ViableT Cells)				
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Dose Categorization (Based on Health Canada Target Dose),[a] n (%)				
Patients received ± 10% planned dose[a]	[redacted]	[redacted]	[redacted]	[redacted]
Below target dose[a] or partial dose, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Received compromised dose,[b] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Weight-Adjusted Axicabtagene Ciloleucel Dose Infused (x 10^6 CAR-positive Viable T cells/kg)				
Mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Conditioning Chemotherapy				
Cyclophosphamide				
Total BSA-adjusted dose (mg/m^2), mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]

	Primary Analysis			
	Phase I (N = 7)	Cohort I (DLBCL) (N = 77)	Cohort II (PMBCL, TFL) (N = 24)	Cohort I and Cohort II (DLBCL, PMBCL, TFL) (N = 101)
Patients received ± 10% planned total dose, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Fludarabine				
Total BSA-adjusted dose (mg/m^2), mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Patients received ± 10% planned total dose, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Re-treatment				
Number re-treated with axicabtagene ciloleucel, n (%)	1 (14)	[redacted]	[redacted]	9 (9)

BSA = body surface area; CAR = chimeric antigen receptor; DLBCL = diffuse large B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

[a] The target dose range was 2 x 10^6 axicabtagene ciloleucel transduced cells per kg body weight, with a maximum of 2 × 10^8 CAR-positive viable T cells.

[b] Compromised dose could mean one of the following: cracked or broken investigational product infusion bag; apheresed cells were not maintained at correct temperature during transport to manufacturing facility; or incoming apheresis product bag compromised with cells exposed to the tubing where bag should have been sealed off.

Source: Information submitted by manufacturer. (CSR, Jan 27. 2017 data cut-off)[32],Locke et al. 2017[36], and Neelapu et al. 2017.[35]

Manufacturing

Overall, there was one manufacturing failure that resulted in the product not being delivered to a study site (see Table 11). The median time from leukapheresis to delivery of the product to the study site was 17 days (range: 14 days to 51 days) (see Table 9).

Table 11: Manufacturing Summary

	Primary Analysis — All Patients			
	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Sample size, N	[redacted]	[redacted]	[redacted]	[redacted]
Axicabtagene ciloleucel delivered to study site, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Frequency of failure to deliver product to study site, n (%)	[redacted]	[redacted]	[redacted]	1 (1)
Reason(s) for failure	[redacted]	[redacted]	[redacted]	[redacted]

DLBCL = diffuse large B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off)[32] and Neelapu et al. 2017.[35]

Critical Appraisal of Pivotal Trial (ZUMA-1)

Internal Validity of Pivotal Trial

The primary limitation of ZUMA-1 was the absence of a comparator or control group against which the treatment benefits and harms of axicabtagene ciloleucel can be compared. The investigators justified the single-arm study design by citing the absence of an effective standard therapy for refractory aggressive large B-cell lymphoma and, therefore, no adequate comparator treatment. The primary end point in ZUMA-1 was tested against a historical control rate of 20%; however, there are a number limitations to this approach. Examples of these limitations include potential differences in the criteria used to define response, potential differences in the timing of assessment of response in ZUMA-1 and the studies used to estimate the historical control rate, and differences in the patient populations in terms of clinical characteristics and standard of care. It should be noted, however, that the statistical analysis of ZUMA-1 incorporated methods to maintain the type I error with multiple testing of ORR in multiple cohorts (i.e., cohort I, and cohort I and II combined) and across multiple time points (i.e., the interim analyses and the primary analysis) for the test of the primary end point in the first 92 patients.

With regard to the primary analysis of ORR, the 20% historical control rate used for comparison in ZUMA-1 was identified by the EMA as an underestimate of objective response in chemo-refractory patients, based on data reported in the SCHOLAR-1 study and a retrospective review.[70] Given that the point estimate from the SCHOLAR-1 meta-analysis was higher than the suggested 20% control rate (i.e., 25.7% [95% CI, 20.9% to 31.3%]), the EMA requested a further analysis to demonstrate that the ORR in ZUMA-1 was also significantly higher than a historical control rate of 26%. To account for the uncertainty of the estimate, the EMA also recommended that the ZUMA-1 results be compared with the upper limit of the CI (i.e., 31.3%). A re-analysis showed that the effect was smaller than that which the manufacturer initially provided but that axicabtagene ciloleucel remained statistically superior to the higher historical control rate.[70]

In the absence of a direct, head-to-head study, indirect treatment comparisons were conducted by the manufacturer to assess the relative treatment benefits of axicabtagene ciloleucel compared with other relevant comparators (Appendix 10 and [redacted]). However, due to the numerous critical limitations that were identified, the potential benefits of axicabtagene ciloleucel compared with salvage chemotherapy or tisagenlecleucel remain unclear.

There were a number of limitations related to the primary end point, ORR. ORR is often used as a measure of response in phase I/phase II drug trials as it can measure antitumour activity. However, it has limitations as an indicator of therapeutic efficacy as it does not provide information on durability of response.[71] Consequently, it cannot be assumed that the ORR of axicabtagene ciloleucel corresponds with long-term duration of effect. In ZUMA-1, ORR was based on the best response each patient achieved before the data cut-off date (and not necessarily at the time of the most recent disease assessment). If a patient's response shifted to a less favourable response category over time, this change was not represented in the ORR and mortality was not accounted for as a competing risk. In ZUMA-1, ORR could improve over the course of the study but could not deteriorate according to the manner in which ORR was defined, measured, and reported; thus, ORR was not a measure of durability of response at any of the analysis points (six months, 12 months, or 24 months). Furthermore, assessments of ORR were not referenced to set time points (i.e., a precise number of months since infusion) but rather to broad periods, where patients had a variable follow-up time (but all patients exceeded the minimum specified). Including longer follow-up times for some patients may have an impact on measures of

efficacy, possibly increasing the opportunity to achieve an ORR. As such, care must be taken not to interpret the ORRs from ZUMA-1 in relation to fixed time points.

The FDA recommends that cancer drug approval be based on direct evidence of clinical benefit — such as improvement in survival, improved quality of life, or improved physical functioning. However, these benefits may not always be predicted by, or correlate with, ORR.[71] Clinically relevant outcomes were reported in ZUMA-1 (e.g., OS, PFS, and DOR), allowing for assessment of durability of response and survival. However, due to the single-arm study design, all outcomes other than ORR were analyzed descriptively. In the absence of a comparator group, time-to-event analyses are difficult to fully interpret and the clinical relevance is unclear.

Another important limitation of ZUMA-1 is the use of investigator disease assessments for the primary analysis. FDA recommends that disease assessments for ORR (and other disease assessment–dependent outcomes such as PFS) be conducted by independent blinded review;[71] this is particularly important in open-label, single-arm studies. ORR based on assessments of disease by IRC was reported in ZUMA-1 as a secondary end point. The use of investigator assessments of disease for the primary analysis can lead to detection bias in the primary end point. The kappa, which measures agreement between the two methods of assessment, indicated fair to moderate agreement at the primary analysis and the 24-month analysis (see Table 34). Further, the concordance between the investigator and IRC assessments was [redacted] at the primary analysis and 81% at the 24-month analysis, demonstrating that approximately [redacted] of patients were classified differently according to the two methods. The ORR based on investigator assessments of disease tended toward better outcomes, as demonstrated by the higher ORR with axicabtagene ciloleucel based on the investigator assessment. Note that the IRC assessments of disease were conducted approximately six weeks earlier than the clinical data cut-off date for the primary analysis. This may have contributed to the observed differences between IRC and investigator assessments of disease. Further, for the analysis of ORR by IRC, there were no preplanned inferential tests of this outcome and no control of the type I error rate, which are major limitations for interpretation of the statistical analysis of the ORR by IRC relative to the historical control rate.

In alignment with the Health Canada Notice of Compliance,[19] the EMA report,[70] and FDA guidance for oncology end points,[71] this current CADTH report focused on IRC-based outcomes to minimize bias. However, not all analyses were available for the IRC data set (e.g., subgroups analyses). In addition, disease assessments for ORR, DOR, and PFS were evaluated per the IWG revised criteria for malignant lymphoma definitions;[69] however, the clinical expert consulted for this review suggested that the use of the Lugano 2014 tumour response criteria would be preferred in a treatment setting.[72] It is unclear what impact the use of the IWG criteria as opposed to the Lugano criteria may have had on the direction or magnitude of the results.

Patients were enrolled in ZUMA-1 on the date of leukapheresis, and thus all enrolled patients were eligible to receive treatment. Since the overall treatment includes leukapheresis, conditioning chemotherapy, and axicabtagene ciloleucel infusion, an analysis based on all enrolled patients would have been informative. The primary and secondary analyses of ZUMA-1 were restricted to the patients who received axicabtagene ciloleucel infusion (i.e., mITT), rather than all enrolled patients for the primary analysis. There were no sensitivity analyses performed with the six-month data based on a full analysis set. This concern, however, was addressed at the 24-month data cut-off with a sensitivity analysis:

patients in the full analysis set (i.e., patients who were leukapheresed but discontinued before axicabtagene ciloleucel infusion) with disease assessments conducted by the IRC. [redacted] that of the mITT analysis set [74%, [redacted] A sensitivity analysis of the Full Analysis Set using IRC assessments of disease at the primary analysis cut-off date was not reported.

Censoring of patients was not applied consistently throughout the analyses and could potentially bias the results, leading to more favourable estimates of the treatment effect associated with axicabtagene ciloleucel. OS was not censored by additional treatments (i.e., chemotherapy, allogeneic SCT while in response or after relapsing from axicabtagene ciloleucel, and re-treatment with axicabtagene ciloleucel). This could potentially bias the estimated treatment effect, producing a more favourable result for axicabtagene ciloleucel. The information about the provision of the additional treatment was insufficiently clear to evaluate the magnitude of the impact of the additional therapy on OS (e.g., whether chemotherapy was administered while in response or after relapsing, what happened to patients after receiving the additional therapy). Censoring for allogeneic SCT differed across the analyses, making comparisons across data cut-offs challenging. At the primary analysis, DOR and PFS using disease assessments by the IRC were not censored for allogeneic SCT received while in response. This could potentially bias the results in favour of axicabtagene ciloleucel. At the 24-month analysis, DOR and PFS were censored for allogeneic SCT received while in response (as per the statistical analysis plan), giving a more accurate indication of the effect of axicabtagene ciloleucel.

It is unclear how AEs were reported over the full course of the study. The protocol states that AEs were recorded from the time of axicabtagene ciloleucel infusion through three months; however, after three months, only targeted AEs and SAEs were reported (e.g., neurological events, hematological events, infections, autoimmune disorders, and secondary malignancies). Therefore, it is difficult to determine if the AEs reported at the 24-month analysis fully captured all categories of AEs. Thus, the AEs reported at the 24-month analysis may not reflect all longer-term adverse effects that patients may experience. Furthermore, despite the planned long-term follow-up of these patients (up to 15 years), AEs are not reported after 24 months; therefore, no additional long-term safety data will be available for axicabtagene ciloleucel in ZUMA-1.

External Validity of Pivotal Trial

The clinical expert consulted for this report assessed the generalizability of the population included in ZUMA-1 to the general Canadian population with r/r large B-cell lymphoma. The clinical expert suggested that some of the inclusion and exclusion criteria may have contributed to the selection of an inherently more clinically stable group of patients, which in turn could influence the study outcomes of ZUMA-1 and the interpretation of the findings of ZUMA-1. For instance, in the opinion of the expert consulted, the inclusion criterion of an ECOG performance status of zero or one may have biased the selection toward more stable patients, compared with patients with an ECOG performance status of two or higher. The use of axicabtagene ciloleucel in patients with an ECOG performance status of two or higher has been reported in the recent literature in clinical practice populations, but experience with patients with an ECOG performance status of two or higher remains limited.[73,74] It is unclear if the results of ZUMA-1 are generalizable to patients with an ECOG performance status of two or higher due to their exclusion from the trial population. As such, the safety and efficacy of axicabtagene ciloleucel in this population remains largely unknown. In addition, the

manufacturer did not identify processes for recruitment; the impact that this has on generalizability is unclear, given the lack of information.

The criteria for organ function and platelet count were identified as restrictive but the clinical expert suggested that this is typical for a clinical trial in this population; nonetheless, this may also contribute to selection bias in terms of a relatively healthier group of patients with r/r large B-cell lymphoma. The clinical expert indicated that by not permitting bridging therapy between leukapheresis and axicabtagene ciloleucel infusion, the patients included in ZUMA-1 may have been more stable (i.e., patients whose disease is sufficiently stable to tolerate the absence of bridging therapy). This may limit the generalizability of the results of ZUMA-1 to a clinical practice setting where bridging therapy may be used to keep the disease stable while waiting for axicabtagene ciloleucel to be manufactured. The median time from leukapheresis to axicabtagene ciloleucel infusion was 23 days, with a range of 15 days to 72 days in phase II of ZUMA-1. According to the clinical expert consulted for this review, bridging chemotherapy may be offered during extended wait times. Indeed, in recent literature, it has been reported that in patients treated with axicabtagene ciloleucel in clinical practice settings, 36%, 56%, and 75% of the patients received bridging therapy.[74-76]

In ZUMA-1, patients received axicabtagene ciloleucel according to a clinical trial protocol. As such, the observed treatment outcomes may not be generalizable to the clinical setting where the possibility exists that longer wait times between leukapheresis and infusion could occur outside the highly regulated and controlled setting of a clinical trial. However, recent reports of patients treated with axicabtagene ciloleucel in the clinical setting have reported the time between leukapheresis and axicabtagene ciloleucel infusion as a median of 26 days (n = 165 infused)[74] and a median of 22 days (range: 19 days to 38 days; n = 22 days infused),[75] suggesting that similar wait times may be observed outside clinical trials. ZUMA-1 also allowed for re-treatment with axicabtagene ciloleucel, which may not be generalizable to clinical practice given that axicabtagene ciloleucel is approved in Canada as a single-dose, one-time treatment.[15]

The population was almost exclusively American (patients were recruited from 21 sites across the US, with one patient from Israel). According to clinical experts consulted for this review, the median age of 58 was younger than may be expected within the Canadian context.[77] There is the potential that axicabtagene ciloleucel would be administered in older patients and that the results of ZUMA-1 may not be generalizable to an older population. The strict eligibility criteria for the level of organ function and functional status may favour more stable patients and may not be generalizable to many of the typical patients with r/r large B-cell lymphomas who do not meet this criteria for end organ function and performance status.[68] The high proportion of patients identified as white in ZUMA-1 may not be generalizable to the ethnicity distribution that may be seen in Canadian patients. In Canada, there is potential for greater diversity — for example, higher proportions of Asian and Indigenous patients. The proportion of patients with an International Prognostic Index greater than two at study entry and the proportion of patients with DLBCL are thought to be reflective of the clinical population, as these patients have very advanced disease, and PMBCL and TFL are rarer large B-cell lymphoma subtypes.

ZUMA-1 did measure some of the outcomes identified by patients as clinically relevant (i.e., response rate, survival, and the need for subsequent treatment) but not all of them (i.e., quality of life, readmission to the hospital, admission to the ICU). Further, health-related quality of life was not measured in phase I and phase II (cohort I and cohort II) of ZUMA-1, which is recommended by the FDA as a more direct indicator of the clinical benefit of cancer

drugs.[71] Furthermore, at the time of this clinical systematic review, only data from the 24-month analysis for ZUMA-1 were available (median follow-up of 23.5 months, range: 0.3 months to 32.4 months [median observation time of 27.1 months]), and some of the time-to-event outcomes were not mature (i.e., DOR, PFS, and OS). Therefore, the benefits of the treatment beyond 24 months are unknown.

Summary of Efficacy and Safety Findings from ZUMA-1 (the Pivotal Trial)

The main body of this report provides the ZUMA-1 findings by IRC of the mITT analysis. The reporting of this analysis set was also used by reviewers at Health Canada for the product monograph.[15] The analyses based on the investigator assessment of disease are provided in Appendix 8, and comparisons between investigator and IRC assessments of disease are provided in Appendix 7 (see Table 34).

The efficacy outcomes are presented from the primary analysis (six-month analysis) and the 24-month analysis (the longest duration of follow-up analyzed; the data cut-off was August 11, 2018). It should be noted, however, that the IRC assessment of disease occurred approximately six weeks earlier than the data cut-off date for the primary analysis (precise date not reported). The analysis of the primary end point corresponds to the date on which the first 92 patients had been followed for at least six months post-axicabtagene ciloleucel infusion. The primary analysis of these 92 patients by the investigator assessment of disease is reported in Appendix 8, Table 40. The primary analysis by IRC (mITT analysis set) included nine additional patients (N = 101) who had been infused with axicabtagene ciloleucel before the primary data cut-off date, but had not yet been followed for six months. The actual follow-up time for patients in ZUMA-1 at each data cut-off is provided in Table 12. With the exception of the primary analysis of the 92 patients by the investigator assessment of disease, all efficacy analyses were based on a sample size of 101 patients. The 24-month analysis included 101 patients, as no new patients were enrolled in cohort I or cohort II, or infused with axicabtagene ciloleucel after the primary data cut-off. The median follow-up time for the 101 patients was [redacted] months at the primary analysis and [redacted] months at the 24-month analysis.

Table 12: Follow-Up Time in ZUMA-1

	Phase I (N = 7)	Cohort I (DLBCL) (N = 77)	Cohort II (PMBCL, TFL) (N = 24)	Cohort I and Cohort II (DLBCL, PMBCL, TFL) (N = 101)
Primary Analysis[a]				
Study follow-up, months, mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Study follow-up, median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Study follow-up, median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]
24-month Analysis[a]				
Study follow-up, months, mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Study follow-up, median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Study follow-up, median (Q1, Q3)	[redacted]	[redacted]	[redacted]	[redacted]

CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; Q1 = first quartile; Q3 = third quartile; TFL = transformed follicular lymphoma.

[a] Actual follow-up time from axicabtagene ciloleucel dosage as time from the first dosage of axicabtagene ciloleucel to date of death or the last date known alive.

Source: For primary analysis — Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off).[32] For 12-month addendum — Information submitted by manufacturer (Clinical Study Report, August 11, 2017).[33] For 24-month analysis — Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off).[34]

Overall Response Rate and Best Overall Response

ZUMA-1 met its primary end point. ORR by investigator assessment in the first 92 patients to be followed for at least six months was 82% (95% CI, 72% to 89%) ($P < 0.0001$) The detailed results for ORR by investigator assessment of disease are provided in Appendix 8 (Table 40). The ORR and the number of patients achieving a CR or PR were more favourable in the investigator assessment of disease compared with the values reported by IRC.

ORR by IRC and the breakdown of the best response at the primary and 24-month analyses are shown in Table 13. At the primary analysis, the ORR by IRC (n = 101) was 71% ([redacted]). In patients who responded to axicabtagene ciloleucel, 52 patients achieved a best response of CR and 20 patients achieved a best response of PR. An additional [redacted] patients achieved a best response of SD and [redacted] patients had progressive disease. The results of the updated ORR by IRC at the 24-month analysis are consistent with the primary analysis (74% [redacted]), with three additional patients achieving an ORR (CR or PR) between the primary and 24-month analyses. At the 24-month analysis, the median time to response among responders (i.e., achievement of CR or PR) was [redacted] month ([redacted]). In total, [redacted] patients had an improvement in response following the initial disease assessment at week four without subsequent therapy; 10 patients who initially had a PR subsequently achieved a best response of CR, seven patients who initially had SD later achieved a best response of CR, and three patients who initially had SD achieved a best response of PR.

Ongoing response is reported in Appendix 7 (Table 35). By the data cut-off date for the primary analysis, [redacted] of patients had an ongoing response of CR or PR as assessed by the IRC. At the 24-month analysis, the ongoing response using disease assessment by the IRC was 36%, with 35 patients having an ongoing CR and one patient having an ongoing PR. A subgroup analysis of ongoing response rate using the investigator assessment of disease at the 24-month analysis is reported in Appendix 8, Table 44.

The subgroup analyses for ORR using the investigator assessment of disease are reported in Appendix 8, Table 41. Results were generally consistent across subgroups and with the main analyses. The ORRs by subgroups were not conducted using IRC assessments of disease.

Table 13: Primary Efficacy Outcome, Objective Response Rate (Independent Central Review Committee)

	Primary Analysis[a]			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Sample size, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IRC ORR (CR + PR), n % (95% CI)[b]	[redacted]	[redacted]	72 71 ([redacted])	[redacted]	[redacted]	75 74 [redacted]
P-value of exact test of IRC ORR ≤ 20%	[redacted]	[redacted]	< 0.0001			
Time to response (CR or PR), median (range), months[c]	[redacted]	[redacted]	NR	[redacted]	[redacted]	[redacted]
Breakdown of Best ORR						
CR, n % (95% CI)	[redacted]	[redacted]	52 51 [redacted]	[redacted]	[redacted]	55 54 [redacted]
PR, n % (95% CI)	[redacted]	[redacted]	20 20 [redacted]	[redacted]	[redacted]	20 20 ([redacted])
SD, n % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD, n % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not done, n % (95% CI)[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CR = complete response; CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; IRC = Independent Central Review Committee; NR = not reported; ORR = objective response rate; PD = progressive disease; PR = partial response; PMBCL = primary mediastinal large B-cell lymphoma; SD = stable disease; TFL = transformed follicular lymphoma.

[a] The IRC's assessment of disease was done approximately six weeks earlier than the clinical data cut-off date for the primary analysis.

[b] 95% CIs determined using the Clopper–Pearson method.

[c] Time to response was only evaluated in those patients who achieved an objective response (CR or PR); sample size was based on number with ORR.

[d] At the primary analysis, disease assessments by IRC were "not done" due to either death before first disease assessment or due to the earlier disease assessments by IRC (compared with the data cut-off date of the primary analysis). At the 24-month analysis, disease assessments by IRC were "not done" due to death before first disease assessment.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off)[32] and Neelapu et al. 2017.[35] For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off),[34] Locke et al. 2019,[37] and Locke et al. 2018.[41]

A preplanned sensitivity analysis of ORR using disease assessment by IRC in the full analysis set (i.e., all enrolled patients) at the 24-month analysis was also performed (see Table 14). The ORR with disease assessments by IRC in the full analysis set was [redacted] than the mITT analysis set ([redacted]). A sensitivity analysis of ORR in the full analysis set at the primary cut-off was not conducted.[78]

Table 14: Sensitivity Analysis for Objective Response Rate (Independent Central Review Committee), Full Analysis Set

		24-Month Analysis	
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Sample size, N	[redacted]	[redacted]	[redacted]
ORR (CR + PR), n (%; 95% CI)[a]	[redacted]	[redacted]	[redacted]
Breakdown of Best ORR			
CR, n (%; 95% CI)	[redacted]	[redacted]	[redacted]
PR, n (%; 95% CI)	[redacted]	[redacted]	[redacted]
SD, n (%; 95% CI)	[redacted]	[redacted]	[redacted]
PD, n (%; 95% CI)	[redacted]	[redacted]	[redacted]
Not done, n (%; 95% CI)[b]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ORR = objective response rate; PD = progressive disease; PR = partial response; PMBCL = primary mediastinal large B-cell lymphoma; SD = stable disease; TFL = transformed follicular lymphoma.

[a] 95% CIs determined using the Clopper–Pearson method.

[b] At the primary analysis, disease assessments by IRC were "not done" due to either death before first disease assessment or due to the earlier disease assessments by IRC (compared with the data cut-off date of the primary analysis). At the 24-month analysis, disease assessments by IRC were "not done" due to death before first disease assessment.

Source: Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off).[34]

Time-to-Event End Points

DOR and PFS using disease assessments by IRC in cohort I and cohort II combined are reported in Table 15. A more detailed breakdown of these secondary outcomes, including the results for cohort I and cohort II reported separately, can be found in Appendix 7, Table 36. At the 24-month analysis, DOR and PFS were censored for patients who had undergone allogeneic SCT while in response, but the primary analyses were not censored for this reason. At the primary analysis, the KM median DOR using disease assessments by IRC was 5.4 months (95% CI, 3.5 months to non-estimable [NE] months), and the estimated proportion of patients in response at six months was 49.8% (95% CI, 32.9% to 64.6%). The KM median DOR using disease assessments by IRC had not been reached at the time of the 24-month analysis but the lower bound of the 95% CI for the estimate was 10.9 months. The estimated proportion of patients in response at 24 months post-axicabtagene ciloleucel infusion was [redacted] based on IRC assessment. For patients who achieved a best response of CR, the proportion of patients in CR at 24 months post-axicabtagene ciloleucel infusion was estimated to be [redacted] (Table 16). This highlights the difference in durability of response between patients who achieved a best response of CR versus a best response of PR, with the KM median duration of PR being [redacted], whereas the KM median duration of CR had not yet been reached.

At the primary analysis, the KM median PFS (i.e., experiencing SD, PR, or CR) using disease assessment by IRC was [redacted]). The estimated proportion of patients with PFS at six months was 44.7% (95% CI, 33.2% to 55.6%). At the 24-month analysis, the KM median PFS (i.e., experiencing SD, PR, or CR) using disease assessments by IRC was [redacted] The estimated proportion of patients with PFS at 24 months was [redacted] A subgroup analysis of PFS rates using disease assessments by IRC at the primary data cut-off is available in Appendix 7: Additional Data for Main Analysis (Table 37). PFS rate estimates were consistent across subgroups and with the main analysis.

DOR and PFS using investigator assessments of disease (Table 42) and the subgroup analyses of PFS using investigator assessments (Table 43) can be found in Appendix 8. DOR and PFS by the investigator assessments of disease were consistent with the values reported by IRC.

Table 15: Secondary Clinical Effectiveness Outcomes (Independent Central Review Committee Committee)

	Primary Analysis[a]	24-Month Analysis
	Cohort I and Cohort II (DLBCL, PMBCL, TFL) (N = 101)	**Cohort I and Cohort II (DLBCL, PMBCL, TFL) (N = 101)**
DOR[b]		
Number of patients with response (CR or PR) by cut-off date	[redacted]	75
Number of patients censored, n (%)	[redacted]	[redacted]
DOR (CR or PR) time, KM median (95% CI), months	[redacted]	NE (10.9 to NE)
Type of Events (Resulting in End of Response)		
Disease progression, n	[redacted]	[redacted]
Disease- or treatment-related death, n	[redacted]	[redacted]
Censoring Reason		
Response ongoing (CR or PR) at cut-off date, n	[redacted]	[redacted]
Started new anticancer therapy, n	[redacted]	[redacted]
Axicabtagene ciloleucel re-treatment before progressive disease	[redacted]	[redacted]
Allogeneic SCT while in response	[redacted]	[redacted]
Percentage of patients in response (KM estimate) at 6 months, % (95% CI)[c]	[redacted]	[redacted]
Percentage of patients in response (KM estimate) at 24 months, % (95% CI)	[redacted]	[redacted]
PFS[d]		
Number of patients	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]
PFS time, KM median (95% CI), months	[redacted]	[redacted]
Type of Events (Resulting in End of PFS)		
Disease progression, n	[redacted]	[redacted]
Disease- or treatment-related death, n	[redacted]	[redacted]

	Primary Analysis[a]	24-Month Analysis
	Cohort I and Cohort II (DLBCL, PMBCL, TFL) (N = 101)	Cohort I and Cohort II (DLBCL, PMBCL, TFL) (N = 101)
Censoring Reason		
Response ongoing, n	[redacted]	[redacted]
Started new anticancer therapy, n	[redacted]	[redacted]
Response not yet assessed, n	[redacted]	[redacted]
Axicabtagene ciloleucel re-treatment before progressive disease, n	[redacted]	[redacted]
Allogeneic SCT, n	[redacted]	[redacted]
Percentage of patients (KM estimate) with PFS at 6 months, % (95% CI)[d]	[redacted]	[redacted]
Percentage of patients (KM estimate) with PFS at 24 months, % (95% CI)	[redacted]	[redacted]

CI = confidence interval; CR = complete response; CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; KM = Kaplan–Meier; NA = not applicable; NE = not estimable; PFS = progression-free survival; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

[a] The Independent Central Review Committee's assessment of disease was done approximately six weeks earlier than the clinical data cut-off date for the primary analysis.

[b] DOR was defined only for patients with objective response and was the time from the first objective response to disease progression or to death due to disease relapse or drug-related toxicity. In the primary analysis, DOR was censored for ongoing response or the start of new anticancer therapy (*excluding* SCT). In the 24-month analysis, DOR was censored for ongoing response, the start of new anticancer therapy (*including* SCT received while in response), or re-treatment with axicabtagene ciloleucel received before the progression of disease.

[c] Differences in KM estimates of DOR and PFS at six months are due to different censoring rules applied to the data.

[d] PFS was defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression or death from any cause. In the primary analysis, PFS was censored for ongoing response, the start of new anticancer therapy (excluding SCT), or response not yet assessed. In the 24-month analysis, PFS was censored for ongoing response, the start of new anticancer therapy (including SCT), or re-treatment received before progression of disease.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off).[32] For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Table 16: Duration of Response in Patients With Best Overall Response of Complete Response (Independent Central Review Committee)

	24-Month Analysis
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Number of patients with response	[redacted]
DOR time (min., max.), months	[redacted]
DOR–CR time, KM median (95% CI), months	NE (NE to NE)
Type of Events (Resulting in End of Response)	
Disease progression, n	[redacted]
Disease- or treatment-related death, n	[redacted]
Number of patients censored, n (%)	[redacted]
Censoring Reason	
Response ongoing (CR or PR) at cut-off date, n	[redacted]
Started new anticancer therapy, n	[redacted]
Axicabtagene ciloleucel re-treatment before progressive disease, n	[redacted]
Allogeneic SCT while in response, n	[redacted]

	24-Month Analysis
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Percentage of patients in CR (KM estimate) at month 3,% (95% CI)	[redacted]
Percentage of patients in CR (KM estimate) at month 6, % (95% CI)	[redacted]
Percentage of patients in CR (KM estimate) at month 12, % (95% CI)	[redacted]
Percentage of patients in CR (KM estimate) at month 24, % (95% CI)	[redacted]

CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; KM = Kaplan–Meier; NA = not applicable; NE = not estimable; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response; TFL = transformed follicular lymphoma.

Source: Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Figure 4: Duration of Response by Best Objective Response Group: Complete Response Versus Partial Response (Independent Central Review Committee)

DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; NE = not estimable; PMBCL = primary mediastinal large B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

Note: Patients in phase II, cohort I and cohort II (DLBCL, PMBCL, TFL) (N = 75). [redacted]

Source: For 24-month analysis — Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Overall Survival

The KM median OS had not been reached by the 24-month data analysis for the combined cohort I and cohort II (NE; 95% CI, 12.8 months to NE months) (Table 17). The KM estimate of the percentage of patients with an OS at the 24-month analysis was 50.5% (95% CI, 40.4% to 59.7%). [redacted]

OS rate by subgroup at the data cut-off for the 24-month analysis is reported in Appendix 7 (Table 38). Results were generally consistent across subgroups and with the main analysis.

Table 17: Overall Survival

	Primary Analysis, All Patients			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	101
Number of patients censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51 (50)
OS, KM median (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NE (12.8 to NE)
Estimate of OS at month 6 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimate of OS at month 12 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimate of OS at month 24 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50.5 (40.4 to 59.7)

CI = confidence interval; CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; KM = Kaplan–Meier; NA = not applicable; NE = not estimable; OS = overall survival; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off) and Neelapu et al. 2017.[35] For 24-month Analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off) and Locke et al. 2019.[37]

A sensitivity analysis of OS in the full analysis set (i.e., all enrolled patients) is reported in Table 18. [redacted]

Table 18: Sensitivity Analysis for Overall Survival, Full Analysis Set

	24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Overall Survival			
Number of patients	[redacted]	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]	[redacted]
OS, KM median (95% CI), months	[redacted]	[redacted]	[redacted]
Estimate of OS at month 6 (95% CI)	[redacted]	[redacted]	[redacted]
Estimate of OS at month 12 (95% CI)	[redacted]	[redacted]	[redacted]
Estimate of OS at month 24 (95% CI)	[redacted]	[redacted]	[redacted]

CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; KM = Kaplan–Meier; NE = not estimable; OS = overall survival; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Source: Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off).[34]

The Need for Subsequent Treatment

Patients were eligible to be re-treated with axicabtagene ciloleucel if they initially demonstrated a response (i.e., PR or CR) followed by disease progression at least three months post-infusion. In total, 10 patients were re-treated with axicabtagene ciloleucel: one patient in phase I and nine patients in phase II (Table 19). At one month following re-treatment, two patients had a CR and four patients had a PR. Re-treatment results were only available based on the investigator assessment of disease, as treatment decisions were based on the investigator assessment of disease and not based on disease assessments by the IRC.

Table 19: Re-treatment With Axicabtagene Ciloleucel (Investigator Assessment)

	Primary Analysis			
	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II, (DLBCL, PMBCL, TFL)
Sample size, N	[redacted]	[redacted]	[redacted]	[redacted]
Re-treatment With Axicabtagene Ciloleucel				
Number re-treated, n (%)[a]	1 (14)	[redacted]	[redacted]	9 (9)
Response to re-treatment at 1 month				
CR, n (%)	[redacted]	[redacted]	[redacted]	2 (22)
PR, n (%)	[redacted]	[redacted]	[redacted]	3 (33)
SD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
PD, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
NA, n (%)	[redacted]	[redacted]	[redacted]	1 (11)

CR = complete response; DLBCL = diffuse large B-cell lymphoma; NA = not applicable; PD = progressive disease; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response; SD = stable disease; TFL = transformed follicular lymphoma.

Note: The source of the second bag of axicabtagene ciloleucel was the second bag from the first lot (n = 3), and the second lot from the frozen cells (n = 6). No new leukapheresis occurred, but new manufacturing of the product occurred in six cases.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off),[32] Locke et al. 2017,[36] Neelapu et al. 2017,[35] and FDA.[68]

The number of patients who received subsequent anticancer therapies following treatment with axicabtagene ciloleucel, as determined by IRC, is reported in Table 20. In total, 10 patients received a subsequent allogeneic SCT post-axicabtagene ciloleucel infusion; [redacted] No patients received a subsequent autologous SCT. Subsequent therapies as determined by the investigator assessment are reported in Appendix 8 (Table 45); this includes [redacted] patients who received subsequent chemotherapy (not reported in the IRC data). The absolute number of allogeneic SCTs received was the same between the two reporting methods; however, whether the SCT was received while in response, after relapsing, or in stable disease differed.

Table 20: Subsequent Therapies (Independent Central Review Committee)

	24-Month Analysis	
	Phase I	**Cohort I and Cohort II, (DLBCL, PMBCL, TFL)**
Sample size, N	[redacted]	[redacted]
Subsequent Anticancer Therapy		
Subsequent chemotherapy, n (%)	[redacted]	[redacted]
Autologous SCT (received while in remission after axicabtagene ciloleucel), n (%)	[redacted]	0 (0)
Allogeneic SCT (received while in remission after axicabtagene ciloleucel), n (%)	[redacted]	[redacted]
Autologous SCT (received while relapsing post-axicabtagene ciloleucel), n (%)	[redacted]	[redacted]
Allogeneic SCT (received while relapsing post-axicabtagene ciloleucel), n (%)	[redacted]	[redacted]
Allogeneic SCT (received while in stable disease post-axicabtagene ciloleucel), n (%)	[redacted]	[redacted]

DLBCL = diffuse large B-cell lymphoma; NR = not reported; PMBCL = primary mediastinal large B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

Note: The Independent Central Review Committee's assessment of disease per Cheson et al. (2007) was used.[69]

Source: Information submitted by manufacturer (manufacturer response, February 1, 2019; data cut-off not reported),[79] Neelapu et al. 2017,[35] and Locke et al. 2019.[37]

Persistence of Chimeric Antigen Receptor T Cells

The blood levels of CAR T positive cells until 24 months post-infusion are reported in Table 21. Levels of CAR T positive cells peaked at a median of [redacted]) post-axicabtagene ciloleucel infusion, and the median peak level of CAR T positive cells was [redacted] cells/μL (range: 0.84 to 1,513 cells/μL). At month six and month 24, the median level of CAR T positive cells had fallen to [redacted], respectively. However, at 24 months, approximately [redacted] of patients were missing from the analysis.

Table 21: Blood Levels of Chimeric Antigen Receptor T Cells

	24-Month Analysis
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Sample size, N	101
Blood Levels of CAR T Positive Cells[a]	
Baseline	
N	[redacted]
Median (range), cells/μl	[redacted]
Day 7	

	24-Month Analysis
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
N	[redacted]
Median (range), cells/µl	[redacted]
Week 2	
N	[redacted]
Median (range), cells/µl	[redacted]
Week 4	
N	[redacted]
Median (range), cells/µl	2.1 (0.0 to 167.4)[c]
Month 3	
N	[redacted]
Median (range), cells/µl	0.4 (0.0 to 28.4)
Month 6	
N	[redacted]
Median (range), cells/µl	[redacted]
Month 9	
N	[redacted]
Median (range), cells/µl	[redacted]
Month 12	
N	[redacted]
Median (range), cells/µl	[redacted]
Month 15	
N	[redacted]
Median (range), cells/µl	[redacted]
Month 18	
N	[redacted]
Median (range), cells/µl	[redacted]
Month 24	
N	[redacted]
Median (range), cells/µl	[redacted]

CAR = chimeric antigen receptor; DLBCL = diffuse large B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Note: Data are from the safety analysis set (i.e., all patients treated with any dose of axicabtagene ciloleucel).

[a] The lower limit of detection of the quantitative polymerase chain reaction assay was 0.001% anti-CD19 CAR T cells/peripheral blood mononuclear cells. The following formula was used to derive the number of anti-CD19 CAR T cells in blood = (white blood cell count/µL)*([% monocyte count + % lymphocyte count]/100)*(qPPB/100).

[b] One patient had monocyte and lymphocyte cell counts of 0.0 cells/µL at day seven, which resulted in an anti-CD19 CAR T-cell level of 0.0 cells/µL when using the calculation listed in footnote a.

[c] One patient had a white blood cell count of 0.0 cells/µL at week four, which resulted in an anti-CD19 CAR T-cell level of 0.0 cells/µL when using the calculation listed in footnote a.

Source: Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off)[34] and FDA.[68]

Harms

All AEs that were observed by the investigator or reported by the patient that occurred after enrolment (i.e., leukapheresis) through three months post-axicabtagene ciloleucel infusion were recorded. After three months, only targeted AEs and SAEs (e.g., neurological, hematological, infections, autoimmune disorders, and secondary malignancies) were recorded for 24 months after treatment, or until disease progression. The definitions and measurement methods for AEs, SAEs, and notable harms are provided in Table 5.

All patients who were treated with axicabtagene ciloleucel experienced at least one AE by the data cut-off for the primary analysis. At the 24-month analysis, 98% of patients had experienced an AE grade of 3 or higher (Table 22). A summary of the most frequently reported treatment-emergent AEs (i.e., AEs that occurred after the start of conditioning chemotherapy; cut-off was 10% or more of patients) is reported in Appendix 7 (Table 39). Frequently reported AEs that were severe (i.e., AEs of grade 3 or higher reported in 10% or more of patients) are reported in Table 23. At the primary analysis, the most common severe AEs were anemia, neutropenia, febrile neutropenia, decreased neutrophil count, and decreased white blood cell count. By the data cut-off for the primary analysis, SAEs were experienced by 53% of patients, 44% of whom experienced grade 3 or higher and 8% of whom experienced grade 5. By the 24-month analysis, the most frequently reported SAEs were encephalopathy, lung infection, pyrexia, febrile neutropenia, and pneumonia (Table 24). No patients withdrew from the study due to AEs. Two patients developed a secondary malignancy, but this was not considered to be related to axicabtagene ciloleucel.

Table 22: Summary of Adverse Events and Secondary Malignancies (Safety Analysis Set)

	Primary Analysis	24-Month Analysis
	Phase I and Phase II	**Phase I and Phase II**
Sample size, N	[redacted]	**108**
Any AE		
Patients with ≥ 1 AE, n (%)	[redacted]	108 (100)
Grade 5, n (%)	[redacted]	9 (8)
Due to disease progression, n (%)	NR	[redacted]
Grade ≥ 3, n (%)	[redacted]	106 (98)
Any conditioning chemotherapy–related AE, n (%)	[redacted]	[redacted]
Conditioning chemotherapy–related AE, grade ≥ 3, n (%)	[redacted]	[redacted]
Any axicabtagene ciloleucel–related AE, n (%)	[redacted]	107 (99)
Axicabtagene ciloleucel–related AE, grade ≥ 3, n (%)	[redacted]	71 (66)
SAEs		
Patients with ≥ 1 SAE, n (%)	[redacted]	60 (56)
Grade 5, n (%)	[redacted]	9 (8)
Due to disease progression, n (%)	[redacted]	[redacted]
Grade ≥ 3, n (%)	[redacted]	52 (48)
Any conditioning chemotherapy–related SAE, n (%)	[redacted]	[redacted]
Conditioning chemotherapy–related SAE, grade ≥ 3, n (%)	[redacted]	[redacted]
Any axicabtagene ciloleucel–related SAE, n (%)	[redacted]	[redacted]

	Primary Analysis	24-Month Analysis
	Phase I and Phase II	Phase I and Phase II
Sample size, N	[redacted]	**108**
Axicabtagene ciloleucel–related SAE, grade ≥ 3, n (%)	[redacted]	[redacted]
WDAE		
WDAE	[redacted]	NR
Development of Secondary Malignancy		
Myelodysplastic syndrome, not related to axicabtagene ciloleucel	2 (2)	2 (2)

AE = adverse event; CSR = Clinical Study Report; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off),[32] Locke et al. 2017,[36] and Neelapu et al.2017.[35]

For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Table 23: Select Treatment-Emergent Adverse Events (Safety Analysis Set)

	Primary Analysis				24-Month Analysis			
	Phase I and Phase II				Phase I and Phase II			
Sample size, N	**108**				**108**			
Most common AEs[a] with grade ≥ 3, n (%)	**All Grades**	**Grade 3**	**Grade 4**	**Grade 5**	**All Grades**	**Grade 3**	**Grade 4**	**Grade 5**
Anemia	71 (66)	44 (41)	3 (3)	0 (0)	73 (68)	46 (43)	3 (3)	0 (0)
Neutropenia	47 (44)	9 (8)	33 (31)	0 (0)	48 (44)	10 (9)	32 (30)	0 (0)
Febrile neutropenia	39 (36)	33 (31)	2 (2)	0 (0)	39 (36)	33 (31)	2 (2)	0 (0)
Neutrophil count decreased	34 (31)	6 (6)	28 (26)	0 (0)	36 (33)	7 (6)	28 (26)	0 (0)
White blood cell count decreased	33 (31)	4 (4)	27 (25)	0 (0)	33 (31)	3 (3)	28 (26)	0 (0)
Thrombocytopenia	36 (33)	11 (10)	15 (14)	0 (0)	38 (35)	11 (10)	15 (14)	0 (0)
Encephalopathy	39 (36)	22 (20)	2 (2)	0 (0)	40 (37)	23 (21)	2 (2)	0 (0)
Lymphocyte count decreased	22 (20)	2 (2)	20 (19)	0 (0)	22 (20)	2 (2)	20 (19)	0 (0)
Hypophosphatemia	31 (29)	19 (18)	2 (2)	0 (0)	31 (29)	18 (17)	2 (2)	0 (0)
Pyrexia	93 (86)	17 (16)	0 (0)	0 (0)	94 (87)	15 (14)	0 (0)	0 (0)
Platelet count decreased	29 (27)	8 (7)	8 (7)	0 (0)	32 (30)	8 (7)	9 (8)	0 (0)
Leukopenia	18 (17)	4 (4)	12 (11)	0 (0)	20 (19)	5 (5)	13 (12)	0 (0)
Hypotension	63 (58)	14 (13)	1 (1)	0 (0)	63 (58)	14 (13)	1 (1)	0 (0)
Hypoxia	33 (31)	12 (11)	1 (1)	0 (0)	34 (31)	11 (10)	1 (1)	0 (0)
Hyponatremia	37 (34)	12 (11)	0 (0)	0 (0)	38 (35)	12 (11)	0 (0)	0 (0)

AE = adverse event; CSR = Clinical Study Report.

[a] Frequency of AE with grade ≥ 3 occurring in ≥ 10% of patients in phase I and phase II combined. Notable harms (i.e., cytokine release syndrome, infections, cytopenias, and neurological events) occurring in ≥ 5% are listed in the notable AEs section.

Source: For primary analysis — Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off).[32] For 24-month analysis — Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off).[34]

Table 24: Detailed Summary of Specific Serious Adverse Events (Safety Analysis Set)

	Primary Analysis				24-Month Analysis			
	Phase I and Phase II				Phase I and Phase II			
Sample size, N	108				108			
Most common SAEs,[a] n (%)	**All Grades**	**Grade 3**	**Grade 4**	**Grade 5**	**All Grades**	**Grade 3**	**Grade 4**	**Grade 5**
Encephalopathy	19 (18)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lung infection	[redacted]	[redacted]	[redacted]	[redacted]	8 (7)	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	8 (7)	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	6 (6)	[redacted]	[redacted]	[redacted]
B-cell lymphoma	5 (5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]	5 (5)	[redacted]	[redacted]	[redacted]
Aphasia	[redacted]	[redacted]	[redacted]	[redacted]	4 (4)	[redacted]	[redacted]	[redacted]
Atrial fibrillation	4 (4)	[redacted]	[redacted]	[redacted]	4 (4)	[redacted]	[redacted]	[redacted]
Cardiac arrest	3 (3)	[redacted]	[redacted]	[redacted]	4 (4)	[redacted]	[redacted]	[redacted]
Urinary tract infection	4 (4)	[redacted]	[redacted]	[redacted]	4 (4)	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]	3 (3)	[redacted]	[redacted]	[redacted]
Agitation	2 (2)	[redacted]	[redacted]	[redacted]	3 (3)	[redacted]	[redacted]	[redacted]
Ejection fraction decreased	4 (4)	[redacted]	[redacted]	[redacted]	3 (3)	[redacted]	[redacted]	[redacted]
Hypotension	3 (3)	[redacted]	[redacted]	[redacted]	3 (3)	[redacted]	[redacted]	[redacted]
Hypoxia	3 (3)	[redacted]	[redacted]	[redacted]	3 (3)	[redacted]	[redacted]	[redacted]
Somnolence	3 (3)	[redacted]	[redacted]	[redacted]	3 (3)	[redacted]	[redacted]	[redacted]
Atrial flutter	2 (2)	[redacted]	[redacted]	[redacted]	2 (2)	[redacted]	[redacted]	[redacted]
Bacteremia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Delirium	[redacted]	[redacted]	[redacted]	[redacted]	2 (2)	[redacted]	[redacted]	[redacted]
Escherichia bacteremia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mental status changes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Myelodysplastic syndrome	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lactic acidosis	2 (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CSR = Clinical Study Report; SAE = serious adverse event.

[a] SAEs in ≥ two patients in phase I and phase II combined, reported in either the primary analysis or 24-month analysis.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off). For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off), Locke et al. 2019,[37] European Medicines Agency,[18] and FDA.[68]

Notable Harms

The characteristics of specific notable harms (as pre-specified in the protocol for this systematic review in Table 1) are summarized in Table 25. CRS was reported in 93% of patients, with 11% of patients experiencing grade 3 or higher CRS. The median time to onset of CRS was [redacted] days, with a median duration of [redacted] days. Neurological events were reported in [redacted] of patients, with 32% of patients experiencing a neurological event of grade 3 or higher and [redacted] of patients experiencing a neurological event that was categorized as a SAE with grade 3 or higher. The median time to onset for neurological events was five days (range: one day to 17 days), with a median duration of [redacted]). The other notable harms of interest — infections, febrile neutropenia, and hypogammaglobulinemia due to B-cell aplasia — were reported in [redacted] 36%, and 16% of patients, respectively.

Table 25: Specific Notable Adverse Events After Axicabtagene Ciloleucel Infusion (Safety Analysis Set)

	Primary Analysis		Primary Analysis		24-Month Analysis	
	Phase I		Cohort I and Cohort II (DLBCL, PMBCL, TFL)		Phase I and Phase II	
Sample size, N	7		101		108	
	Any	**Grade ≥ 3**	**Any**	**Grade ≥ 3**	**Any**	**Grade ≥ 3**
CRS,[a] n (%)						
Any	6 (86)	1 (14)	94 (93)	13 (13)	100 (93)	12 (11)
Number of patients for whom events resolved, n (%)	[redacted]	[redacted]	93 (99)	[redacted]	98 (91)	[redacted]
Time to onset (days), median (range)	[redacted]	[redacted]	2 (1 to 12)	[redacted]	2 (1 to 12)	[redacted]
Duration among patients whose symptoms resolved (days), median (range)	7 (3 to 17)	[redacted]	8 (NR)	[redacted]	[redacted]	[redacted]
Time to resolution to grade ≤ 1, days, median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptoms of CRS						
Pyrexia	5 (71)	1 (14)	77 (76)	11 (11)	[redacted]	[redacted]
Hypotension	3 (43)	1 (14)	41 (41)	9 (9)	44 (44)	10 (10)
Hypoxia	1 (14)	1 (14)	22 (22)	9 (9)	[redacted]	[redacted]
Tachycardia	2 (29)	0 (0)	21 (21)	1 (1)	24 (24)	1 (1)
Chills	[redacted]	[redacted]	20 (20)	0 (0)	[redacted]	[redacted]
Sinus tachycardia	[redacted]	[redacted]	8 (8)	0 (0)	[redacted]	[redacted]
Headache	1 (14)	0 (0)	5 (5)	0 (0)	[redacted]	[redacted]
Infections, n (%)						
Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30 (28)
Type of infection						
Bacterial infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Opportunistic infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Primary Analysis		Primary Analysis		24-Month Analysis	
	Phase I		Cohort I and Cohort II (DLBCL, PMBCL, TFL)		Phase I and Phase II	
Sample size, N	7		101		108	
	Any	**Grade ≥ 3**	**Any**	**Grade ≥ 3**	**Any**	**Grade ≥ 3**
Other infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-Cell Aplasia, n (%)						
Hypogammaglobulinemia secondary to B-cell aplasia, any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypogammaglobulinemia	[redacted]	[redacted]	[redacted]	[redacted]	16 (15)	0 (0)
Blood immunoglobulin G decreased	[redacted]	[redacted]	[redacted]	[redacted]	2 (2)	0 (0)
Cytopenias, n (%)						
Any (thrombocytopenia, neutropenia, anemia)	[redacted]	[redacted]	[redacted]	[redacted]	100 (93)	93 (86)
Prolonged thrombocytopenia[c]	[redacted]	[redacted]	[redacted]	[redacted]	49 (45)	32 (30)
Type of cytopenia						
Thrombocytopenia	2 (29)	2 (29)	[redacted]	[redacted]	38 (35)	26 (24)
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]	32 (30)	17 (16)
Febrile neutropenia	4 (57)	4 (57)	[redacted]	[redacted]	39 (36)	35 (32)
Neutropenia	3 (43)	3 (43)	[redacted]	[redacted]	48 (44)	42 (39)
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	36 (33)	35 (32)
Anemia	2 (29)	2 (29)	[redacted]	[redacted]	73 (68)	49 (45)
Neurological Events, n (%)						
Any[d]	6 (86)	4 (57)	65 (64)	28 (28)	72 (67)	35 (32)
Serious neurological event, any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients for whom events resolved, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to onset (days), median (range)	[redacted]	[redacted]	5 (1 to 17)	[redacted]	5 (1 to 17)	[redacted]
Duration among patients whose symptoms resolved (days), median (range)[a]	8 (2 to 20)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to resolution to grade ≤ 1, days, median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of event						
Encephalopathy	5 (71)	3 (42)	34 (34)	21 (21)	40 (37)	25 (23)
Confusional state	[redacted]	[redacted]	29 (29)	9 (9)	29 (27)	10 (9)
Tremor	4 (57)	1 (14)	29 (29)	1 (1)	33 (31)	2 (2)
Aphasia	1 (14)	0 (0)	18 (18)	7 (7)	19 (18)	8 (7)
Somnolence	3 (43)	2 (29)	15 (15)	7 (7)	18 (17)	9 (8)
Agitation	1 (14)	1 (14)	9 (9)	4 (4)	10 (9)	5 (5)
Memory impairment	[redacted]	[redacted]	7 (7)	1 (1)	8 (7)	0 (0)
Mental status changes	[redacted]	[redacted]	6 (6)	2 (2)	7 (6)	3 (3)
Hallucination	1 (14)	0 (0)	[redacted]	[redacted]	5 (5)	0 (0)

	Primary Analysis		Primary Analysis		24-Month Analysis	
	Phase I		Cohort I and Cohort II (DLBCL, PMBCL, TFL)		Phase I and Phase II	
Sample size, N	7		101		108	
	Any	**Grade ≥ 3**	**Any**	**Grade ≥ 3**	**Any**	**Grade ≥ 3**
Dysarthria	[redacted]	[redacted]	[redacted]	[redacted]	5 (5)	2 (2)

CRS = cytokine release syndrome; CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; NA = not applicable; NR = not reported; PMBCL = primary mediastinal large B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

Note: Symptoms of notable harms reported if present in ≥ 5% of patients in phase I and phase II combined. Percentages were calculated using the total number of patients in the treatment group as the denominator.

[a] Percentages of "CRS — Any" were calculated using the total number of patients as the denominator. Percentages of individual symptoms of CRS (e.g., pyrexia) were calculated using the total number of patients with any CRS as the denominator.

[redacted]

[c] Defined as the longest consecutive duration of thrombocytopenia ≥ 30 days.

[d] One event occurred prior to infusion of axicabtagene ciloleucel.

[redacted]

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off),[32] Locke et al. 2017,[36] and Neelapu et al. 2017.[35]
For 24-month Analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off),[34] Locke et al. 2019,[37] and FDA.[68]

Other Outcomes

Management of Adverse Effects

The use of concomitant medications administered after axicabtagene ciloleucel to treat CRS, neurologic events, and other conditions (not specified in the ZUMA-1 protocol) are reported in Table 26. The use of tocilizumab was the most commonly reported concomitant medication, reported as used by 86% of patients in phase I and 43% of patients in phase II. Steroids were the second most commonly used concomitant medication (used by 57% of phase I patients and [redacted] of phase II patients).

Table 26: Concomitant Medications of Interest

	24-Month Analysis			
	Phase I	**Cohort I (DLBCL)**	**Cohort II (PMBCL, TFL)**	**Cohort I and Cohort II (DLBCL, PMBCL, TFL)**
Sample size, N	7	[redacted]	[redacted]	[redacted]
Steroids[a]				
Any	4 (57)	[redacted]	[redacted]	[redacted]
Used for treatment of CRS	[redacted]	[redacted]	[redacted]	[redacted]
Used for treatment of neurologic event	[redacted]	[redacted]	[redacted]	[redacted]
Other use	[redacted]	[redacted]	[redacted]	[redacted]
Tocilizumab				
Any	6 (86)	[redacted]	[redacted]	43 (43)
Used for treatment of CRS	[redacted]	[redacted]	[redacted]	[redacted]
Used for treatment of neurologic event	[redacted]	[redacted]	[redacted]	[redacted]
Other use	[redacted]	[redacted]	[redacted]	[redacted]
Vasopressors[b]				
Any	[redacted]	[redacted]	[redacted]	17 (17)
Used for treatment of CRS	[redacted]	[redacted]	[redacted]	[redacted]
Used for treatment of neurologic event	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Other[c]				
Any	[redacted]	[redacted]	[redacted]	[redacted]
Used for treatment of CRS	[redacted]	[redacted]	[redacted]	[redacted]
Used for treatment of neurologic event	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

	24-Month Analysis			
	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Sample size, N	7	[redacted]	[redacted]	[redacted]
Immunoglobulins[d]				
Any	[redacted]	[redacted]	[redacted]	[redacted]

CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; NOS = not otherwise specified; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Note: Concomitant medications were medications that started on or after first axicabtagene ciloleucel dose start date, and started on or prior to discharge date of initial hospitalization period, except for immunoglobulin, for which all immunoglobulin uses started on or after the first axicabtagene ciloleucel dose were included.

[a] Steroid category includes the following: hydrocortisone sodium succinate, dexamethasone sodium phosphate, neodecadron, prednisolone sodium phosphate, methylprednisolone sodium succinate, triamcinolone diacetate, triamcinolone hexacetonide, dexamethasone, budesonide, betamethasone, betamethasone sodium phosphate, celestona bifas, prednisolone butylacetate, hydrocortisone, cortisone acetate, prednisone, methylprednisolone acetate, dexamethasone acetate, dexamethasone sodium succinate, fludrocortisone acetate, paramethasone acetate, hydrocortisone acetate, hydrocortisone sodium phosphate, triamcinolone acetonide, methylprednisolone, prednisolone acetate, prednisolone.

[b] Vasopressors category includes the following: epinephrine hydrochlorid, metaraminol tartrate, dobutamine hydrochloride, epinephrine, epinephrine bitartrate, dopamine hydrochloride, norepinephrine bitartrate, ephedrine, midodrine hydrochloride, norepinephrine hydrochloride, isoprenaline sulphate, hydroxyamphetamine hydrobromide, methoxamine hydrochloride, mephentermine sulphate, desmopressin acetate, lypressin, vasopressin, vasopressin tannate, amrinone lactate, milrinone lactate, phenylephrine.

[c] "Other" category includes the following: Rilonacept; secukinumab, etanercept, tacrolimus monohydrate, adalimumab, azathioprine sodium, anakinra, mycophenolate mofetil, mycophenolate sodium, abatacept, tacrolimus, infliximab, cyclosporine, basiliximab, siltuximab.

[d] Immunoglobulin category includes the following: immunoglobulin human normal, immunoglobulins NOS, immunoglobulin G human, Polygam S/D, kipferon.

Source: Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off),[34] Locke et al. 2017,[36] Neelapu et al. 2017,[35] and Locke et al. 2019.[37]

Mortality

By the 24-month analysis, the proportion of patients who died after axicabtagene ciloleucel infusion was 50% in phase II. Of those who died in phase II, 30 of the deaths occurred before the data cut-off for the primary analysis, and the other 20 deaths occurred between the dates for the primary analysis and the 24-month analysis. The most common cause of death was progression of disease. Mortality was attributed to the treatment in two patients.

Table 27: Mortality

	Primary Analysis				24-Month Analysis			
	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Sample size (number of infused patients), N	7	77	24	101	7	77	24	101
Total number of deaths after enrolment, n/N (%)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of deaths after	4 (57)	[redacted]	[redacted]	30 (30)	4 (57)	[redacted]	[redacted]	50 (50)

	Primary Analysis				24-Month Analysis			
	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
axicabtagene ciloleucel infusion (all-cause mortality), n (%)								
Treatment-related mortality, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2 (2)
Deaths that occurred ≤ 30 days after infusion	1 (14)	[redacted]	[redacted]	2 (2)	[redacted]	[redacted]	[redacted]	2 (2)
Deaths that occurred > 30 days through 3 months (92 days) after infusion	1 (14)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths that occurred > 3 months (92 days) after infusion	2 (29)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary Cause of Death, n (%)								
Adverse event	1 (14)	[redacted]	[redacted]	3 (3)	1 (14)	[redacted]	[redacted]	3 (3)
Progressive disease	3 (43)	[redacted]	[redacted]	25 (25)	3 (43)	[redacted]	[redacted]	43 (43)
Other [b]	0 (0)	[redacted]	[redacted]	2 (2)	[redacted]	[redacted]	[redacted]	4 (4)

CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; NR = not reported; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

[a] Includes patients who were enrolled but never infused with axicabtagene ciloleucel.

[b] The four patients with the cause of death noted as "other" died after disease progression and after receiving subsequent cancer therapy.

Source: For primary analysis — Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off).[32] For 24-month Analysis — Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off),[34] Locke et al. 2019,[37] European Medicines Agency,[18] and National Institute for Health and Care Excellence.[80]

Resource Utilization

Hospitalization Following Infusion

The duration of hospitalization following axicabtagene ciloleucel infusion is presented in Table 28. As per the protocol, all patients were hospitalized to receive treatment with axicabtagene ciloleucel and were expected to remain in hospital for at least seven days following axicabtagene ciloleucel infusion. Health care resource utilization post-discharge was not reported (e.g., number of readmissions or admissions to the ICU, emergency department visits, or other urgent care visits).

Additional concomitant procedures that patients received following axicabtagene ciloleucel infusion are reported in Table 29.

Table 28: Duration of Hospitalization

	Primary Analysis			
	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]
Total duration of hospitalization for the axicabtagene ciloleucel infusion, days, mean (standard deviation)	[redacted]	[redacted]	[redacted]	[redacted]
Total duration of hospitalization for the axicabtagene ciloleucel infusion, days, median (range)	[redacted]	[redacted]	[redacted]	[redacted]

DLBCL = diffuse large B-cell lymphoma; ICU = intensive care unit; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Note: Data are from the safety analysis set (i.e., all patients treated with any dose of axicabtagene ciloleucel).

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off).[32]

Table 29: Concomitant Procedures (Modified Intention-to-Treat)

	Primary Analysis			
	Phase I	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II, (DLBCL, PMBCL, TFL)
Sample size, N	7	77	24	101
Procedure, n (%)				
Cytological test of effusion/ ascites	[redacted]	[redacted]	[redacted]	[redacted]
MRI	[redacted]	[redacted]	[redacted]	[redacted]
Examination of cerebrospinal fluid	[redacted]	[redacted]	[redacted]	[redacted]
Endotracheal intubation	[redacted]	[redacted]	[redacted]	[redacted]
Dialysis	[redacted]	[redacted]	[redacted]	[redacted]
Mechanical ventilation	[redacted]	[redacted]	[redacted]	[redacted]
Other[a]	[redacted]	[redacted]	[redacted]	[redacted]

CT = computed tomography; DLBCL = diffuse large B-cell lymphoma; MRI = magnetic resonance imaging; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Note: Procedures done during re-treatment period were excluded.

[a] "Other" category includes brain MRI, CT head, CT brain, and CT sinus scans.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off).[32]

Indirect Treatment Comparisons

Complete details regarding the characteristics, critical appraisal, and results of the indirect comparisons (alongside their critical appraisal) are provided in Appendix 10: Comparison of Axicabtagene Ciloleucel to Salvage Chemotherapy (ZUMA-1 to SCHOLAR-1) and Appendix 11.

The manufacturer conducted and submitted two indirect treatment comparison studies: [redacted][81] and an indirect comparison of axicabtagene ciloleucel versus salvage chemotherapy.[82] [redacted][81] For the indirect comparison of axicabtagene ciloleucel versus salvage chemotherapy, the manufacturer conducted standardized analyses and propensity score analyses [redacted][82]

- [redacted]
- Key limitations for the comparison between axicabtagene ciloleucel and salvage chemotherapy include: [redacted] and considerable heterogeneity between the study populations that cannot be controlled in the analyses.

Summary of Evidence-Based Guideline

Research Question #3:

What are the evidence-based clinical practice guidelines for the use of axicabtagene ciloleucel for the treatment of adults with eligible types of relapsed or refractory non-Hodgkin lymphoma?

Characteristics of the Evidence-Based Guideline

One evidence-based guideline was identified regarding the use of axicabtagene ciloleucel for the treatment of adults with eligible types of r/r large B-cell lymphoma.[83] The guideline was developed by the National Comprehensive Cancer Network (NCCN) and contained recommendations for the diagnosis and treatment of B-cell lymphomas, including DLBCL. The target population for the guideline is therefore patients with B-cell lymphoma, and the intended users of the guideline are all individuals who impact decision-making in cancer care, including physicians, nurses, pharmacists, payers, patients and their families, and many others. The development of the guideline followed the NCCN process, which includes a literature search, critical review of the evidence, and consensus from a multidisciplinary panel.[84] The characteristics of the guideline are presented in Table 30.

Table 30: Characteristics of Evidence-Based Clinical Practice Guideline for Chimeric Antigen Receptor T-Cell Therapy

Guideline			Methodology		
Intended Users, Target Population, Country of Development	**Intervention, Major Outcomes Considered**	**Evidence Collection, Selection, and Synthesis**	**Evidence Quality Assessment**	**Recommendations Development and Evaluation**	**Guidelines Validation**
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): B-Cell Lymphomas, Version 2.2019 Section for patients with relapse/ refractory DLBCL					
Intended users: The NCCN Guidelines are intended to assist all individuals who impact decision-making in cancer care, including physicians, nurses, pharmacists, payers, patients and their families, and many others. **Target population:** B-cell lymphomas **Country of development:** US	**Intervention:** Axicabtagene ciloleucel **Major outcomes considered:** Complete response or partial response	An electronic search of the PubMed database was performed for key literature on DLBCL, primary mediastinal large B-cell lymphoma, double-hit lymphoma, and gray zone lymphoma. The following article types were included: clinical trial, phase II, phase III, or	The panel considered the following factors during deliberations regarding the level of evidence: quality of data (e.g., trial design and how the results/ observations were derived [RCTs, non-RCTs, meta-analyses or systematic reviews, clinical case reports, case series]); quantity of data (e.g., number of trials, size of trials, clinical observations only); and consistency of data (e.g., similar or conflicting results across available studies or observations). The degree of consensus	Recommendations for which high-level evidence was lacking were derived from critical evaluation of available evidence, integrated with the clinical expertise and consensus of a multidisciplinary panel of cancer specialists, clinical experts, and researchers. The panel was charged with evaluating the efficacy of treatment, utility of tests or evaluations, and toxicity of the various interventions. The panel deliberated on the interpretation of the clinical evidence and voted on how the evidence should be incorporated into the	Not reported

Guideline			Methodology		
Intended Users, Target Population, Country of Development	**Intervention, Major Outcomes Considered**	**Evidence Collection, Selection, and Synthesis**	**Evidence Quality Assessment**	**Recommendations Development and Evaluation**	**Guidelines Validation**
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): B-Cell Lymphomas, Version 2.2019 Section for patients with relapse/ refractory DLBCL					
		phase IV; Guideline; RCT; meta-analyses; systematic reviews; and validation studies. PubMed search yielded 108 citations; data from key PubMed articles and articles from additional sources deemed as relevant have been included the guideline.	was based on the percentage of panel votes. **NCCN Evidence Categories** **Category 1**: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. All recommendations are category 2A unless otherwise indicated.	existing guidelines. Panel chair and panel members developed the wording of the recommendations.	

DLBCL = diffuse large B-cell lymphoma; NCCN = National Comprehensive Cancer Network; RCT = randomized controlled trial.

Source: NCCN B-cell lymphoma guideline (2018)[83] and Development and Update of the NCCN Guidelines (accessed January 30, 2019).[84]

Critical Appraisal of Evidence-Based Guideline

Based on the *Appraisal of Guidelines for Research and Evaluation II* assessment criteria,[27] the guideline was of overall high quality. The scope and purpose of the guideline were well defined, including the overall objective of the guideline and the population to whom the guideline was intended to apply, although the health questions covered by the guideline were not explicitly described. General information on the NCCN Guidelines' panel was referenced;[84] however, specific panel membership was not reported so it is not possible to assess the degree to which stakeholders were involved, and it was not reported whether the guideline was sent for stakeholder feedback. Literature search methods and some inclusion criteria were described; however, the interventions and outcomes that were considered were not explicitly defined. General methods for formulating recommendations are provided on the NCCN website;[84] methods specific to these recommendations, though, were not clearly described. Supporting evidence for health benefits, side effects, and risks was presented.

However, there was no explicit discussion regarding the balance of benefits and harms and there was no explicit link between the evidence and the recommendations. Detailed algorithms were provided that indicated courses of treatment by disease type and severity; however, when alternative treatment options were available (e.g., axicabtagene ciloleucel versus tisagenlecleucel), the guidelines did not clearly describe how to choose among the different alternatives. Barriers and facilitators to applying the guideline were not described, and whether potential resource implications of applying the recommendations had been considered was not reported. Competing interests of members of the guideline development group were recorded and addressed. According to the general methods for NCCN Guidelines, the guidelines underwent institutional review prior to publication. NCCN Guidelines are updated on a regular basis to ensure that recommendations take into account the most current evidence. The guideline was scheduled to be updated in August 2019.[85]

Summary of Evidence-Based Guideline Recommendations

A summary of the evidence-based recommendations regarding the use of axicabtagene ciloleucel for the treatment of adults with eligible types of r/r large B-cell lymphoma from the NCCN Guidelines are presented in Table 31: Summary of Key Recommendations for Chimeric Antigen Receptor T-Cell Therapy. In all recommendations of CAR T-cell therapy, the guideline specifies axicabtagene ciloleucel or tisagenlecleucel, but does not provide further guidance regarding the selection of CAR T-cell therapy.

Table 31: Summary of Key Recommendations for Chimeric Antigen Receptor T-Cell Therapy

Recommendation	Strength of Recommendation
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): B-Cell Lymphomas, Version 2.2019	
Patients with histological transformation of follicular lymphoma to DLBCL If patient has partial response to therapy: • axicabtagene ciloleucel or tisagenlecleucel (only after ≥ 2 prior chemoimmunotherapy regimens, if not previously given; patients should have received at least 1 anthracycline or anthracenedione-based regimen, unless contraindicated). If patient has no response or progressive disease: • axicabtagene ciloleucel or tisagenlecleucel (only after ≥ 2 prior chemoimmunotherapy regimens; patients should have received at least 1 anthracycline or anthracenedione-based regimen, unless contraindicated). **Patients with histologic transformation of follicular lymphoma to DLBCL after multiple lines of prior therapies** If patient has relapsed or progressive disease: • axicabtagene ciloleucel or tisagenlecleucel (only after ≥ 2 prior chemoimmunotherapy regimens, if not previously given; patients should have received at least 1 anthracycline or anthracenedione-based regimen, unless contraindicated). If patient has partial response to subsequent therapy following relapse or progressive disease: • axicabtagene ciloleucel or tisagenlecleucel (only after ≥ 2 prior chemoimmunotherapy regimens, if not previously given; patients should have	Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Recommendation	Strength of Recommendation
received at least 1 anthracycline or anthracenedione-based regimen, unless contraindicated). **Patients with relapsed or refractory DLBCL** If patient has partial response to second-line therapy: • as consolidation/additional therapy (third line) — axicabtagene ciloleucel or tisagenlecleucel or • if patient has had 2 relapses or more — axicabtagene ciloleucel or tisagenlecleucel (if not previously given). **Patient selection** • Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy, including DLBCL, NOS; primary mediastinal large B-cell lymphoma; high-grade B-cell lymphoma; and DLBCL arising from follicular lymphoma. • Health care facilities that dispense and administer axicabtagene ciloleucel must be enrolled and comply with the Risk Evaluation and Mitigation Strategies requirements.	

DLBCL = diffuse large B-cell lymphoma; NCCN = National Comprehensive Cancer Network; NOS = not otherwise specified.

Source: NCCN B-cell lymphoma guideline (2018).[83]

Discussion

Adults with r/r large B-cell lymphoma currently have few treatment options available and there is a need for effective therapies. Standard treatment options include salvage chemotherapies, immunotherapy, radiation therapy, and SCT, none of which produce long-term survival benefits.[1,4,14] Recently, two CAR T-cell therapies have been approved for use in Canada.[19,86] Tisagenlecleucel was reviewed separately by CADTH and appears to have a clinical benefit, but uncertainties remain, including limited long-term data regarding efficacy and safety.[87] Axicabtagene ciloleucel was approved for use by Health Canada in February 2019[19] in adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Axicabtagene ciloleucel is an approved treatment option that could potentially meet this unmet clinical need in adult patients with r/r large B-cell lymphoma who have failed at least two previous lines of treatment. The pivotal trial of axicabtagene ciloleucel in adults with r/r large B-cell lymphoma, ZUMA-1, met its primary end point and demonstrated a significantly greater ORR as per the investigator assessment of disease (82%) relative to a pre-specified 20% historical control. This was true whether disease assessments were done by the investigators (82%) or an independent review committee (71%). However, it is important to consider the limitations of ORR (as measured and analyzed in ZUMA-1) that were highlighted in this report when interpreting this finding.

Key secondary outcomes demonstrated an estimated OS of 50.5% (95% CI, 40.4% to 59.7%) at 24 months, [redacted]. Evidence of efficacy from the conference abstracts in which axicabtagene ciloleucel was administered in a clinical setting demonstrated similar results, with response rates ranging from 64% to 86% across four studies.[73-75,88] However, evidence from these abstracts was limited to follow-up times of one

or four months, no information was available on duration of response, and it was unclear whether these patients met the Health Canada–approved indication for axicabtagene ciloleucel.[73-75,88]

AEs with axicabtagene ciloleucel were common, with all patients in ZUMA-1 experiencing at least one AE, with CRS and cytopenias being the most frequent. While CRS was experienced by 93% of patients, 11% were grade 3 or higher. CRS events resolved in all but two patients with a median duration of seven days. There were proportionately more severe cases for other notable harms. Specifically, neurological events were reported in 67% of patients, with 32% of patients experiencing events of grade 3 or higher. The majority of neurological events resolved, with a median duration of symptoms of 13 days. Cytopenias were reported in 93% of patients (86% with grade 3 or higher), and no information was reported regarding duration of symptoms or whether cytopenias resolved. Events of CRS reported in the literature from the abstracts of seven studies conducted in clinical settings were comparable to that observed in ZUMA-1, with the prevalence of any grade of CRS ranging from 83% to 100%, and the prevalence of CRS of grade 3 or higher ranging from zero to 17%.[73-75,89-92] Neurological events reported in the abstracts of three studies that administered axicabtagene ciloleucel in a clinical setting were also similar to the results seen in ZUMA-1 (any grade, 76%; grade ≥ 3, 38%).[73-75]

Clinical expert consultation indicated that there were some concerns regarding the inclusion and exclusion criteria of ZUMA-1 that could potentially limit the generalizability of the findings to the larger target population with r/r large B-cell lymphoma. Specifically, it was noted that the population may have been a younger and more stable group of patients relative to patients with r/r large B-cell lymphoma in Canadian clinical practice. Furthermore, not permitting bridging therapy limits the generalizability to real-world practice and could impact clinical outcomes, although the nature and extent of such an impact is unknown.

The main limitation of this review was that the primary source of evidence was generated from one open-label, single-arm, non-randomized study. Non-randomized studies are inherently weaker and prone to multiple biases as compared with randomized studies. The reliance on investigator assessments of disease introduced additional bias to the open-label study; however, the inclusion of disease assessments by IRC as secondary outcomes likely reduced some of this outcome assessment–related bias.

The single-arm study design precludes head-to-head comparison with other treatments for r/r large B-cell lymphoma and, thus, does not inform the relative efficacy and safety of axicabtagene ciloleucel compared with other interventions. With the exception of indirect comparisons of axicabtagene ciloleucel with tisagenlecleucel and with salvage chemotherapy, no comparative data were available for axicabtagene ciloleucel in patients with r/r large B-cell lymphoma relative to other treatment alternatives. [redacted][81][redacted][82][redacted] This uncertainty was also reflected in the evidence-based clinical practice guideline from the NCCN; in all recommendations for CAR T-cell therapy, the NCCN guideline specifies axicabtagene ciloleucel or tisagenlecleucel, but does not provide further guidance regarding selection of CAR T-cell therapy.[83] Nonetheless, the NCCN Guidelines[83] do recommend CAR T-cell therapy as a course of treatment per the Health Canada indication for axicabtagene ciloleucel.[15] To better inform the comparative effectiveness of axicabtagene ciloleucel,

further studies that directly compare axicabtagene ciloleucel to other CAR T-cell therapies, such as tisagenlecleucel, are needed.

There were a number of limitations with the assessment of the response related to ZUMA-1. The reliance on investigator assessments of disease had the potential to introduce bias in the assessment of outcomes, which can be compounded by the open-label study. The inclusion of disease assessments by IRC as secondary outcomes may have provided a more objective assessment of outcomes despite the open-label design; however, no statistical analyses of IRC outcomes were a priori specified inferential analyses. There was discordance between the two methods of assessment, with kappa values indicating fair to moderate agreement, and approximately 20% of patients classified differently according to the two methods. The ORR by investigator assessments of disease tended toward better outcomes, suggesting bias in these assessments. In addition, the assessment of efficacy was not conducted at a set time but rather to a broad period of time, with the primary inferential analysis of ORR occurring when 92 patients had been followed for "at least six months" after axicabtagene ciloleucel infusion, rather than a uniform point in time post-infusion for all patients.

When interpreting the findings of this review, it is important to consider that while the ORR demonstrated that axicabtagene ciloleucel did induce an anticancer response, this may not always correlate with survival.[71] From a clinical perspective, PFS, DOR, and the ongoing response at the primary analysis and the 24-month analysis are likely to be more informative concerning durability of response. While an objective response to axicabtagene ciloleucel was reported in 72 patients (52 with CR and 20 with PR), at some point prior to the primary data cut-off, some of these patients experienced a response that was transient, as fewer patients were reported to have an ongoing complete or partial response at the time of the primary analysis (43 patients with ongoing response; 43% of all treated patients, or 60% of all responders). By the 24-month analysis, 36 patients had an ongoing response to axicabtagene ciloleucel (36% of all treated patients, or 48% of all responders), of which 35 were complete responders. This demonstrates that among patients who did respond to axicabtagene ciloleucel, nearly half experienced an ongoing CR at least 24 months after infusion. Furthermore, in the clinical setting, there is variability in the ORR for axicabtagene ciloleucel reported in abstracts, with lower, comparable, and higher response rates reported;[73-75,88] this supports the importance of looking beyond ORR as the measure of effectiveness.

PFS may be particularly useful to assess clinical effectiveness, as it accounts for transient responders and mortality. In ZUMA-1, the pivotal trial, 50% of the patients survived without disease progression for at least nine months, and the estimated proportion of patients surviving without disease progression at 24 months was 41%. For patients who achieved a best response of CR, the estimated proportion of patients having a CR at 24 months was [redacted] demonstrating the durability of response in complete responders. Durable, long-term remission of disease (i.e., no disease at 24 months) was identified through patient input as an important treatment outcome for patients with large B-cell lymphoma. The findings for PFS and duration of CR at 24 months suggest that, for some patients, axicabtagene ciloleucel may help them reach this important outcome.

A life unimpeded by their disease was identified as an important outcome by patients; however, treatment with axicabtagene ciloleucel did not prevent the need for subsequent treatment in all patients, with 10 patients requiring re-treatment with axicabtagene ciloleucel (conditions for re-treatment are outlined in Table 2), [redacted] patients requiring subsequent

chemotherapy, and 10 patients receiving an allogeneic SCT ([redacted]). Patients who received subsequent anticancer therapies were censored from the analyses for DOR and PFS at 24 months. Therefore, further information about the impact of these subsequent treatments on these patients is unknown.

Subgroup analyses generally yielded consistent findings across subgroups, although the estimated OS differed by lymphoma subtype, with higher estimated OS at 24 months in patients with PMBCL or TFL compared with patients with DLBCL ([redacted]). However, these subgroup analyses were intended to evaluate the robustness and consistency of the treatment effects, and were not for clinical decision-making. The sample sizes of individual subgroups were small and the analyses were intended to be used for descriptive purposes, rather than for making inferences about efficacy.

The primary gaps in the evidence for axicabtagene ciloleucel are the absence of data that directly compares axicabtagene ciloleucel with other treatments used in r/r large B-cell lymphoma; the absence of long-term efficacy and safety data (i.e., more than two years); the lack of patient-reported outcomes, such as health-related quality of life; and the lack of data on hospitalization (e.g., hospital readmission, length of stay, admission to the ICU), which patient input had identified as important.

In the literature, one study abstract reported hospital readmissions in 22% of patients, and ICU care in 30% of patients in the clinical setting,[73] suggesting that these outcomes should be considered for axicabtagene ciloleucel. Ongoing follow-up for phase II, as well as additional cohorts in ZUMA-1 (e.g., cohort III), will likely contribute longer-term results as well as health-related quality of life outcomes (a list of ongoing clinical trials is presented in Appendix 12). There are also challenges associated with generalizing findings from the US to the Canadian context, and a lack of evidence of effectiveness and safety among patients who are older or less stable (e.g., patients who receive bridging therapy, or with an ECOG performance status of two or more). In addition, no real-world evidence was identified that used commercial axicabtagene ciloleucel in patients who definitively meet the Health Canada indication for axicabtagene ciloleucel. The study abstracts identified while conducting review suggest that more detailed, fully published, peer-reviewed evidence from other countries regarding the potential benefits and harms of commercial axicabtagene ciloleucel may soon be available, but it is not currently possible to ascertain whether the patients included in these abstracts were eligible to receive axicabtagene ciloleucel, according to the approved Health Canada indication.[52,73-76,88-93]

Conclusion

The efficacy findings from ZUMA-1 suggested that in adults with r/r large B-cell lymphoma, treatment with axicabtagene ciloleucel resulted in a demonstrable ORR, and that 50% of patients treated with axicabtagene ciloleucel survived without disease progression for at least nine months. However, axicabtagene ciloleucel has the potential to exert severe AEs. At the time of this review, the median OS and DOR had not been reached for the pivotal ZUMA-1 trial. Therefore, longer-term follow-up, comparative data, and clinical experience will be required to fully understand the benefit–risk profile for axicabtagene ciloleucel and its place in therapy in r/r large B-cell lymphoma.

References

1. Leukemia & Lymphoma Society of Canada. About blood cancers: facts and statistics. 2018; http://www.llscanada.org/disease-information/facts-and-statistics. Accessed 2018 Sept 14.
2. Health technology appraisal: axicabtagene ciloleucel for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma. Final scope. London (GB): National Institute for Health and Care Excellence; 2017: https://www.nice.org.uk/guidance/gid-ta10214/documents/final-scope. Accessed 2019 Mar 21.
3. U.S. Food and Drug Administration. News release: FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma 2017; https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm581216.htm. Accessed 2018 Sep 12.
4. Lulla PD, Hill LC, Ramos CA, Heslop HE. The use of chimeric antigen receptor T cells in patients with non-Hodgkin lymphoma. *Clin Adv Hematol Oncol.* 2018;16(5):375-386.
5. Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. *Nat Rev Clin Oncol.* 2018;15(1):31-46.
6. Canadian Cancer Society. Non-Hodgkin lymphoma: diffuse large B-cell lymphoma. 2018; http://www.cancer.ca/en/cancer-information/cancer-type/non-hodgkin-lymphoma/non-hodgkin-lymphoma/diffuse-large-b-cell-lymphoma/?region=bc#ixzz5DiMO0Zkc. Accessed 2018 Nov 15.
7. Lymphoma Canada. Understanding diffuse large B cell lymphoma (DLBCL). 2018; https://www.lymphoma.ca/DLBCL. Accessed 2018 Nov 15.
8. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood.* 2017;130(16):1800-1808.
9. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol.* 2015;33(6):540-549.
10. Wang HI, Smith A, Aas E, et al. Treatment cost and life expectancy of diffuse large B-cell lymphoma (DLBCL): a discrete event simulation model on a UK population-based observational cohort. *Eur J Health Econ.* 2017;18(2):255-267.
11. Raut LS, Chakrabarti PP. Management of relapsed-refractory diffuse large B cell lymphoma. *South Asian J Cancer.* 2014;3(1):66-70.
12. Chimeric antigen receptor T-cell therapy for B-cell cancers: effectiveness and value. Final evidence report. Boston (MA): Institute for Clinical and Economic Review; 2018: https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Final_Evidence_Report_032318.pdf. Accessed 2018 Mar 23.
13. Link BK, Maurer MJ, Nowakowski GS, et al. Rates and outcomes of follicular lymphoma transformation in the immunochemotherapy era: a report from the University of Iowa/MayoClinic Specialized Program of Research Excellence Molecular Epidemiology Resource. *J Clin Oncol.* 2013;31(26):3272-3278.
14. Nair R, Neelapu SS. The promise of CAR T-cell therapy in aggressive B-cell lymphoma. *Best Pract Res Clin Haematol.* 2018;31(3):293-298.
15. Yescarta™ (axicabtagene ciloleucel): suspension for intravenous infusion [product monograph]. Mississauga (ON): Gilead Sciences Canada Inc.; 2019 Feb 13: https://pdf.hres.ca/dpd_pm/00049621.PDF. Accessed 2019 Jun 14.
16. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med.* 2014;6(224):224ra225.
17. Committee For Medicinal Products For Human Use. Yescarta axicabtagene ciloleucel [initial authorisation]. *(Summary of opinion)*. London (GB): European Medicines Agency; 2018: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/004480/WC500251207.pdf. Accessed 2018 Sep 13.
18. Yescarta (axicabtagene ciloleucel). London (GB): European Medicines Agency; 2018: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004480/human_med_002292.jsp&mid=WC0b01ac058001d124. Accessed 2018 Sep 14.
19. Health Canada. Notice of compliance (NOC) for Yescarta. 2019; https://health-products.canada.ca/noc-ac/index-eng.jsp. Accessed 2019 Mar 25.
20. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2018 Aug 10.
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
22. Zorzela L, Loke YK, Ioannidis JP, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ.* 2016;352:i157.
23. Axicabtagene ciloleucel for non-Hodgkin lymphoma: health technology assessment introduction and clinical review protocol. *(CADTH optimal use report: vol. 9, no. 1a)*. Ottawa (ON): CADTH; 2019: https://cadth.ca/sites/default/files/pdf/ct0002-axi-cel-for-clinical-protocol.pdf. Accessed 2019 Mar 27.
24. Kite Pharma. Prescribing information: YESCARTA (axicabtagene ciloleucel). Silver Spring (MD): U.S. Food and Drug Administration; 2017.
25. National Cancer Institute. Complete response. In: NCI dictionary of cancer terms. 2019; https://www.cancer.gov/publications/dictionaries/cancer-terms/def/complete-response. Accessed 2019 Jan 24.
26. Hematologic malignancies: regulatory considerations for use of minimal residual disease in development of drug and biological products for treatment: guidance for industry [draft guidance]. Silver Spring (MD): U.S. Food and Drug Administration; 2018: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM623333.pdf. Accessed 2019 Jan 24.

27. Agree Next Steps Consortium. The AGREE II Instrument. [Hamilton (ON)]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2018 Nov 15.

28. Reeves BC, Wells GA, Waddington H. Quasi-experimental study designs series-paper 5: a checklist for classifying studies evaluating the effects on health interventions-a taxonomy without labels. *J Clin Epidemiol.* 2017;89:30-42.

29. Dekkers OM, Egger M, Altman DG, Vandenbroucke JP. Distinguishing case series from cohort studies. *Ann Intern Med.* 2012;156(1 Pt 1):37-40.

30. Sayre JW, Toklu HZ, Ye F, Mazza J, Yale S. Case reports, case series - from clinical practice to evidence-based medicine in graduate medical education. *Cureus.* 2017;9(8):e1546.

31. Systematic Review and Literature Review Software by Evidence Partners. DistillerSR [software]. 2019; https://www.evidencepartners.com/products/distillersr-systematic-review-software/. Subscription required.

32. Clinical study report: KTE-C19-101 a phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1) [**CONFIDENTIAL** manufacturer's submission]. Santa Monica (CA): Kite Pharma, Inc.; 2017 Jul 28.

33. Clinical study report addendum: 12-month follow-up analysis of ZUMA-1 cohorts 1 and 2. Addendum to module 5.3.5.1 ZUMA-1 clinical study report: KTE-C19-101 a phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1) [**CONFIDENTIAL** manufacturer's submission]. Santa Monica (CA): Kite Pharma, Inc.; 2018 Feb 9.

34. Clinical study report addendum: 24-month follow-up analysis of ZUMA-1 cohorts 1 and 2. Addendum to module 5.3.5.1 ZUMA-1 clinical study report: KTE-C19-101 a phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1) [**CONFIDENTIAL** manufacturer's submission]. Santa Monica (CA): Kite Pharma, Inc.; 2018 Nov 2.

35. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.

36. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 Anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. *Mol Ther.* 2017;25(1):285-295.

37. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. *Lancet Oncol.* 2019;20(1):31-42.

38. Kite, A Gilead Company. NCT02348216: Safety and efficacy of KTE-C19 in adults with refractory aggressive non-hodgkin lymphoma (ZUMA-1). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2015: https://clinicaltrials.gov/ct2/show/study/NCT02348216. Accessed 2019 Apr 29.

39. Neelapu SS, Ghobadi A, Jacobson CA, et al. 2-year follow-up and high-risk subset analysis of ZUMA-1, the pivotal study of axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma. *Blood.* 2018;132(Suppl 1):2967.

40. Locke FL, Bartlett NL, Lekakis LJ, et al. Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma (NHL): long-term follow-up of ZUMA-1. *Br J Haematol.* 2018;181 (Suppl 1):25.

41. Locke FL, Ghobadi A, Jacobson CA, et al. Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma: durability of response in ZUMA-1. *HemaSphere.* 2018;2(Suppl 2):83.

42. Neelapu S, Ghobadi A, Jacobson C, et al. Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma: long-term safety and efficacy of ZUMA-1. *Br J Haematol.* 2019;185(Suppl 1):26-27.

43. Locke FL, Ghobadi A, Lekakis LJ, et al. Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma: outcomes by prior lines of therapy in ZUMA-1. *HemaSphere.* 2018;2(Suppl 2):348.

44. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphomas (NHL): primary results of the pivotal trial ZUMA-1. *Hematol Oncol.* 2017;35(Suppl 2):28.

45. Locke FL, Ghobadi A, Lekakis LJ, et al. Axicabtagene ciloleucel in patients with refractory large B cell lymphoma: outcomes by prior lines of therapy in the pivotal phase 2 study, ZUMA-1. *Clin Lymphoma Myeloma Leuk.* 2018;18:S276.

46. Locke FL, Neelapu SS, Bartlett NL, et al. Clinical and biologic covariates of outcomes in ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL). *Haematologica.* 2017;102(Suppl 2):172.

47. Lundry Locke F, Swarup Neelapu S, Bartlett NL, et al. Clinical and biologic covariates of outcomes in ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (r-NHL). *J Clin Oncol.* 2017;35(15 Suppl 1):7512

48. Gisselbrecht C, Locke FL, Bartlett NL, et al. A comparison of one year outcomes in patients with refractory large B cell lymphoma from ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1. *Br J Haematol.* 2018;181(Suppl 1):72-73.

49. Neelapu SS, Locke FL, Bartlett NL, et al. A comparison of one year outcomes in ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1 in patients with refractory, aggressive non-Hodgkin lymphoma (NHL). *Blood.* 2017;130(Suppl 1):579.

50. Locke FL, Ghobadi A, Jacobson CA, et al. Durability of response in patients with refractory large B cell lymphoma treated with axicabtagene ciloleucel in the pivotal phase 2 study, ZUMA-1. *Clin Lymphoma Myeloma Leuk.* 2018;18:S277-S278.

51. Locke FL, Ghobadi A, Jacobson CA, et al. Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (axi-cel) in patients (pts) with refractory large B cell lymphoma. *J Clin Oncol.* 2018;36(15 Suppl 1):3003.

52. Lin Y, Locke FL, Neelapu SS, et al. Efficacy, safety, and covariates of outcomes with axicabtagene ciloleucel (axi-cel; KTE-C19) from ZUMA-1, a pivotal trial in patients with refractory, aggressive non-Hodgkin lymphoma (NHL). *Hum Gene Ther.* 2017;28(12):A5.

53. Beaupierre A, Patterson A, Kahle N, et al. Interdisciplinary management of chemorefractory NHL patients treated with KTE-C19 (anti-CD19 CAR T cells) in phase 1 of the ZUMA-1 clinical study...Academy of Oncology Nurse & Patient Navigators, November 17-20, 2016, Las Vegas, Nevada. *J Oncol Navig Surviv.* 2016;7(9):56.

54. Neelapu SS, Locke FL, Bartlett NL, et al. KTE-C19 (anti-CD19 CAR T cells) induces complete remissions in patients with refractory diffuse large B-cell lymphoma (DLBCL): results from the pivotal phase 2 ZUMA-1. *Blood.* 2016;128(22).

55. Neelapu SS, Locke FL, Bartlett NL, et al. Ongoing complete remissions (CR) in the phase 1 of ZUMA-1: a phase 1-2 multicenter study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in subjects with refractory aggressive B-cell non-Hodgkin lymphoma (NHL). *J Clin Oncol.* 2016;34(Suppl 15):7559.

56. Locke FL, Neelapu SS, Bartlett NL, et al. Ongoing complete remissions in phase 1 of ZUMA-1: a phase 1-2 multi-center study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B cell non-Hodgkin lymphoma (NHL). *Ann Oncol.* 2016;27(Suppl 6).

57. Neelapu S, Locke F, Bartlett N, et al. Ongoing complete remissions in ZUMA-1: a phase 1-2 multicenter study of KTE-C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B cell non-Hodgkin lymphoma. *Clin Lymphoma Myeloma Leuk.* 2016;16:S102.

58. Locke FL, Ghobadi A, Lekakis LJ, et al. Outcomes by prior lines of therapy (LoT) in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (axi-cel) in patients (pts) with refractory large B cell lymphoma. *J Clin Oncol.* 2018;36(15 Suppl 1):3039

59. Rossi JM, Neelapu SS, Go WY, et al. Phase 1 biomarker analysis of the ZUMA-1 (KTE-C19-101) study: a phase 1-2 multi-center study evaluating the safety and efficacy of anti-CD19 CAR T cells (KTE-C19) in subjects with refractory aggressive non-Hodgkin lymphoma (NHL). *Blood.* 2015;126(23):2730.

60. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 clinical results of the ZUMA-1 (KTE-C19-101) study: a phase 1-2 multi-center study evaluating the safety and efficacy of anti-CD19 CAR T cells (KTE-C19) in subjects with refractory aggressive non-Hodgkin lymphoma (NHL). *Blood.* 2015;126(23):3991.

61. Neelapu SS, Locke FL, Bartlett NL, et al. A phase 2 multicenter trial of KTE-C19 (anti-CD19 CAR T cells) in patients with chemorefractory primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL): interim results from ZUMA-1. *Blood.* 2016;128(22):998.

62. Locke FL, Neelapu SS, Bartlett NL, et al. Primary results from ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axicel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL). *Cancer Res.* 2017;77(13 Suppl 1):CT019.

63. Neelapu SS, Locke FL, Bartlett NL, et al. A standardized comparison of outcomes in patients (pts) with refractory, aggressive non-Hodgkin lymphoma (rNHL) from the SCHOLAR-1 analysis and the ZUMA-1 study of axicabtagene ciloleucel (axi-cel). *Ann Oncol.* 2017;28(Suppl 5):v412.

64. Locke FL, Neelapu SS, Bartlett NL, et al. Updated phase 1 results from ZUMA-1: a phase 1-2 multi-center study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in subjects with refractory aggressive non-Hodgkin lymphoma (NHL). *Mol Ther.* 2016;24(Suppl 1):S294.

65. Ghobadi A, Locke FL, Neelapu SS, et al. Updated phase I results from ZUMA-1: a phase I-II multicenter study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in subjects with refractory aggressive non-Hodgkin lymphoma (NHL). *Cancer Res.* 2016;76(14 Suppl):CT135.

66. Siddiqi T, Neelapu SS, Locke FL, et al. Updated results from ZUMA-1: a phase 1-2 multicenter study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in refractory aggressive B-cell non-Hodgkin lymphoma (NHL). *Haematologica.* 2016;101(Suppl 1):318.

67. Neelapu SS, Locke FL, Ghobadi A, et al. ZUMA-1 pivotal phase 2 trial of axicabtagene ciloleucel (axi-cel, KTE-C19; Anti-CD19 CAR T cells) in patients (pts) with refractory aggressive non-Hodgkin lymphoma (NHL). *Mol Ther.* 2017;25(5 Suppl 1):333.

68. Yescarta (axicabtagene ciloleucel): BLA clinical review memorandum. (STN 125643). Rockville (MD): U.S. Food and Drug Administration (FDA); 2017: https://www.fda.gov/media/109149/download. Accessed 2019 May 15.

69. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579-586.

70. Committee for Medicinal Products for Human Use. Assessment report: Yescarta (axicabtagene ciloleucel). *(European public assessment report)*. London (GB): European Medicines Agency; 2018 Jun 22: https://www.ema.europa.eu/en/documents/assessment-report/yescarta-epar-public-assessment-report_en.pdf. Accessed 2019 Mar 26.

71. Clinical trial endpoints for the approval of cancer drugs and biologics: guidance for industry. Silver Spring (MD): U.S. Food and Drug Administration; 2018: https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf. Accessed 2019 Mar 26.

72. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.

73. Jacobson CA, Hunter B, Armand P, et al. Axicabtagene ciloleucel in the real world: outcomes and predictors of response, resistance and toxicity. *Blood.* 2018;132(Suppl 1):92.

74. Nastoupil LJ, Jain MD, Spiegel JY, et al. Axicabtagene ciloleucel (axi-cel) CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: real world experience. *Blood.* 2018;132(Suppl 1):91.

75. Spiegel JY, Sahaf B, Hossain N, et al. Elevated axicabtagene ciloleucel (CAR-19) expansion by immunophenotyping is associated with toxicity in diffuse large B-cell lymphoma. *Blood.* 2018;132(Suppl 1):576.

76. Byrne MT, Oluwole O, Allen D, et al. Commercial chimeric antigen receptor (CAR) T cells: unfamiliar roads and stalled cars. *Biol Blood Marrow Transplant.* 2019;25(3 Suppl):S302.

77. National Cancer Institute. Cancer stat facts: non-Hodgkin lymphoma. 2019; https://seer.cancer.gov/statfacts/html/nhl.html. Accessed 2019 Apr 29.

78. Gilead Sciences Inc. response to checkpoint meeting questions on axicabtagene ciloleucel [**CONFIDENTIAL** additional manufacturer's information]. Mississauga (ON): Gilead Sciences Inc.; 2019 March 15.

79. Gilead Sciences Canada Inc. response to February1, 2019 CADTH request for additional information [**CONFIDENTIAL** additional manufacturer's information]. Mississauga (ON): Gilead Sciences Canada, Inc.; 2019 Feb 1.

80. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies. *Committee papers*. London (GB): National Institute for Health and Care Excellence; 2018: https://www.nice.org.uk/guidance/ta559/evidence/appraisal-consultation-committee-papers-pdf-6661404973. Accessed 2019 May 15.

81. [redacted]

82. [redacted]

83. NCCN clinical practice guidelines in oncology (NCCN guidelines): B-cell lymphomas. Version 2.2019. Plymouth Meeting (PA): National Comprehensive Cancer Network, Inc.; 2019 Mar 6.

84. National Comprehensive Cancer Network. Development and update of the NCCN guidelines: introduction. In: NCCN guidelines & clinical resources. 2019; https://www.nccn.org/professionals/development.aspx. Accessed 2019 Mar 25.

85. National Comprehensive Cancer Network. NCCN guidelines panels-meeting schedule. In: NCCN guidelines & clinical resources. 2019; https://www.nccn.org/about/meeting_schedule.aspx. Accessed 2019 Mar 25.

86. Health Canada. Regulatory decision summary for Kymriah. 2018; https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?lang=en&linkID=RDS00422. Accessed 2018 Nov 13.

87. Tisagenlecleucel for acute lymphoblastic leukemia and diffuse large B-cell lymphoma: clinical report. *(CADTH optimal use report vol. 8, no. 3c)*. Ottawa (ON): CADTH; 2019: https://cadth.ca/sites/default/files/pdf/car-t/op0538-tisagenlecleucel-clinical-report_jan2019.pdf. Accessed 2019 Mar 27.

88. Oak J, Spiegel JY, Sahaf B, et al. Target antigen downregulation and other mechanisms of failure after axicabtagene ciloleucel (CAR19) therapy. *Blood.* 2018;132(Suppl 1):4656.

89. Faramand R, Kotani H, Morrissey D, et al. Prediction of CAR T-related toxicities in R/R DLBCL patients treated with axicabtagene ciloleucel using point of care cytokine measurements. *Biol Blood Marrow Transplant.* 2019;25(3 Suppl):S408-S409.

90. Nahas G, Komanduri KV, Pereira D, et al. Persistent cytopenias after chimeric antigen receptor T-cell immunotherapy for CD19+ aggressive lymphoma: a single institution experience. *Biol Blood Marrow Transplant.* 2019;25(3 Suppl):S180.

91. Sano D, Nastoupil LJ, Fowler NH, et al. Safety of axicabtagene ciloleucel CD19 CAR T-cell therapy in elderly patients with relapsed or refractory large B-cell lymphoma. *Blood.* 2018;132(Suppl 1):96.

92. Maakaron J, Penza S, El Boghdadly Z, et al. Procalcitonin as a potential biomarker for differentiating bacterial infectious fevers from cytokine release syndrome. *Blood.* 2018;132(Suppl 1):4216.

93. Jim HSL, Hoogland AI, Collier A, Booth-Jones M, Jain MD, Locke FL. Patient-reported and neurocognitive outcomes in patients treated with axicabtagene ciloleucel. *Blood.* 2018;132(Suppl 1):2289.

94. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood.* 2014;124(2):188-195.

95. Lin VW, Jiang Y, Chuang LH, Navale L, Cheng P, Purdum A. Health utilities for patients with relapsed or refractory large B-cell lymphoma (R/R-LBCL): ad hoc analysis from an axicabtagene ciloleucel (axi-cel) safety management study [P889]. *Bone Marrow Transplant.* 2018. https://www.nature.com/articles/s41409-018-0325-z.pdf. Accessed 2019 Mar 21.

96. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. In: Higgins JPT, Green S, eds: The Cochrane Collaboration; 2011: https://handbook-5-1.cochrane.org/. Accessed 2019 Apr 29.

97. Modern epidemiology. In: Rothman KJ, Greenland S, Lash TL, eds. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2008.

98. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.* 2011;46(3):399-424. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3144483/. Accessed 2019 Apr 29.

99. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies. *(NICE appraisal consultation document)*. London (GB): National Institute for Health and Care Excellence; 2018: https://www.nice.org.uk/guidance/gid-ta10214/documents/appraisal-consultation-document. Accessed 2018 Sept 13.

100. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-adjusted indirect comparisons in health technology appraisal. *Med Decis Making.* 2018;38(2):200-211.

101. Phillippo DM, Ades AE, Sofia Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-adjusted indirect comparisons in submissions to NICE. Report by the Decision Support Unit. *(NICE DSU technical support document 18)*. Sheffield (GB): Decision Support Unit, ScHARR, University of Sheffield; 2016: https://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/Population-adjustment-TSD-FINAL.pdf. Accessed 2019 Apr 29.

102. Committee for Medicinal Products for Human Use. Assessment report: Kymriah (tisagenlecleucel). *(European public assessment report)*. London (GB): European Medicines Agency; 2018: https://www.ema.europa.eu/en/documents/assessment-report/kymriah-epar-public-assessment-report_en.pdf. Accessed 2019 Apr 29.

103. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health.* 2012;15(6):940-947.

104. National Institute for Health and Care Excellence. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies *(NICE final appraisal document)*. 2019; https://www.nice.org.uk/guidance/gid-ta10269/documents/final-appraisal-determination-document. Accessed 2019 Apr 29.

105. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. *Res Synth Methods.* 2010;1(3-4):258-271.

106. Latimer N. Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Report by the Decision Support Unit. *(NICE DSU technical support document 14)*. Sheffield (GB): Decision Support Unit, ScHARR, University of Sheffield; 2013: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf. Accessed 2019 Apr 29.

107. Kite, A Gilead Company. NCT03761056: Efficacy and safety of axicabtagene ciloleucel as first-line therapy in participants with high-risk large B-cell lymphoma (ZUMA-12). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/NCT03761056. Accessed 2019 Apr 29.

108. Kite, A Gilead Company. NCT03391466: Efficacy of axicabtagene ciloleucel compared to standard of care therapy in subjects with relapsed/refractory diffuse large B cell lymphoma (ZUMA-7). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/NCT03391466?intr=axicabtagene+ciloleucel+OR+Yescarta+OR+axi-cel+OR+KTEC19+OR+KTE-C19&lupd_s=11%2F29%2F2018&lupd_e=04%2F15%2F2019&rank=3. Accessed 2019 Apr 29.

109. Kite, A Gilead Company. NCT03704298: Safety and efficacy of axicabtagene ciloleucel in combination with utomilumab in adults with refractory large B-cell lymphoma (ZUMA-11). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/NCT03704298. Accessed 2019 Apr 29.

110. Kite, A Gilead Company. NCT02926833: Safety and efficacy of KTE-C19 in combination with atezolizumab in adults with refractory diffuse large B-cell lymphoma (DLBCL) (ZUMA-6). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2016: https://clinicaltrials.gov/ct2/show/NCT02926833. Accessed 2019 Apr 29.

111. Daiichi Sankyo Co, Ltd. JPRN-JapicCTI-183914: A phase 2 multicenter, open-label, single-arm study of KTE-C19 in Japanese patients with refractory or relapsed large B cell lymphoma. International Clinical Trials Registry Platform. Geneva (CH): World Health Organization; 2019: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-JapicCTI-183914. Accessed 2019 Apr 29.

Appendix 1: Literature Search Strategy

Clinical Search

OVERVIEW	
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials EBM Reviews - Cochrane Database of Systematic Reviews EBM Reviews - Database of Abstracts of Reviews of Effects EBM Reviews - Health Technology Assessment database Embase Ovid MEDLINE ALL **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	2018 November
Alerts:	Monthly search updates
Study Types:	Guidelines, health technology assessments, systematic reviews, or meta-analyses filters used
Limits:	None for Drug search CAR-T 2013-present; Indication 2016-present; English, French

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.dq	Candidate Term Word (Embase)
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.nm	Name of Substance; used to search portions of chemical names
.ot	Original Title; includes any non-English titles in the original language
.pt	Publication type
cctr	Ovid database code; Cochrane Central Register of Controlled Trials
coch	Ovid database code; Cochrane Database of Systematic Reviews
dare	Ovid database code; Database of Abstracts of Reviews of Effects
clhta	Ovid database code; Health Technology Assessment database
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY

Search Strategy:

#	Searches
1	(axicabtagene ciloleucel* or Yescarta* or axi-cel or KTEC19* or KTE-C19*).ti,ab,ot,kf,kw,hw,nm.
2	1 use medall
3	1 use cctr
4	Axicabtagene Ciloleucel/
5	(axicabtagene ciloleucel* or Yescarta* or axi-cel or KTEC19* or KTE-C19*).ti,ab,kw,dq.
6	or/4-5
7	6 use oemezd
8	2 or 3 or 7
9	Receptors, Antigen, T-Cell/
10	Antigens, CD19/
11	((chimeric antigen adj3 receptor*) or (chimeric* adj3 (immune* or immunoreceptor* or immuno-receptor*)) or ((artificial or chimeric or engineered or modif*) adj3 (Tcell* or T-cell* or Tlymphocyte* or T-lymphocyte*)) or (CAR adj3 T) or CAR therap* or CART cell* or anti CD19 or anti CD-19 or ((CD19 or CD-19) adj5 (antibod* or anti-bod* or antigen* or anti-gen* or immune* or immunotherap* or immuno-therap* or target* or therap* or Tcell* or T-cell*)) or CART19 or CART-19).ti,ab,kf.
12	or/9-11
13	12 use medall
14	Chimeric Antigen Receptor/
15	Chimeric Antigen Receptor T Cell/
16	Chimeric Antigen Receptor T Cell Immunotherapy/
17	CD19 Antigen/
18	((chimeric antigen adj3 receptor*) or (chimeric* adj3 (immune* or immunoreceptor* or immuno-receptor*)) or ((artificial or chimeric or engineered or modif*) adj3 (Tcell* or T-cell* or Tlymphocyte* or T-lymphocyte*)) or (CAR adj3 T) or CAR therap* or CART cell* or anti CD19 or anti CD-19 or ((CD19 or CD-19) adj5 (antibod* or anti-bod* or antigen* or anti-gen* or immune* or immunotherap* or immuno-therap* or target* or therap* or Tcell* or T-cell*)) or CART19 or CART-19).ti,ab,kw,dq.
19	or/14-18
20	19 use oemezd
21	13 or 20
22	limit 21 to (english or french) [Limit not valid in CDSR,DARE; records were retained]
23	limit 22 to yr="2013 -Current" [Limit not valid in DARE; records were retained]
24	Lymphoma, Non-Hodgkin/
25	exp Lymphoma, B-Cell/
26	Lymphoma, Follicular/
27	(DLBCL or lymphoma* or lymphosarcoma* or lympho-sarcoma* or nonhodgkin* or non hodgkin* or reticulosarcoma* or reticulo-sarcoma* or ((lymphatic* or reticulum-cell*) adj sarcoma*) or PMBCL).ti,ab,kf.
28	((lymphoid* or mediastinal or mediastinum or bcell* or b-cell* or tcell* or t-cell*) adj3 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or metasta*)).ti,kf.
29	or/24-28

MULTI-DATABASE STRATEGY

30 29 use medall
31 Nonhodgkin Lymphoma/
32 B Cell Lymphoma/
33 exp Diffuse Large B Cell Lymphoma/
34 Large Cell Lymphoma/
35 Lymphocytic Lymphoma/
36 Lymphosarcoma/
37 Follicular Lymphoma/
38 (DLBCL or lymphoma* or lymphosarcoma* or lympho-sarcoma* or nonhodgkin* or non hodgkin* or reticulosarcoma* or reticulo-sarcoma* or ((lymphatic* or reticulum-cell*) adj sarcoma*) or PMBCL).ti,ab,kw,dq.
39 ((lymphoid* or mediastinal or mediastinum or bcell* or b-cell* or tcell* or t-cell*) adj3 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or metasta*)).ti,kw.
40 or/31-39
41 40 use oemezd
42 30 or 41
43 limit 42 to (english or french) [Limit not valid in CDSR,DARE; records were retained]
44 limit 43 to yr="2016 -Current" [Limit not valid in DARE; records were retained]
45 1 or 4 or 5
46 45 use coch
47 45 use dare
48 45 use clhta
49 or/9-11,14-18
50 limit 49 to (english or french) [Limit not valid in CDSR,DARE; records were retained]
51 limit 50 to yr="2013 -Current" [Limit not valid in DARE; records were retained]
52 51 use coch
53 51 use dare
54 51 use clhta
55 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
56 (guideline* or standards or consensus* or recommendat*).ti.
57 (practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti.
58 (care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti.
59 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti.
60 (algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti.
61 (algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.
62 or/55-61
63 meta-analysis.pt.
64 meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
65 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.

MULTI-DATABASE STRATEGY	
66	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
67	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
68	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
69	(handsearch* or hand search*).ti,ab,kf,kw.
70	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
71	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
72	(meta regression* or metaregression*).ti,ab,kf,kw.
73	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
74	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
75	(cochrane or (health adj2 technology assessment) or evidence report).jw.
76	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
77	(outcomes research or relative effectiveness).ti,ab,kf,kw.
78	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.
79	(meta-analysis or systematic review).md.
80	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
81	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf,kw.
82	umbrella review*.ti,ab,kf,kw.
83	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
84	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
85	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
86	or/63-85
87	62 or 86
88	23 and 87
89	44 and 62
90	8 or 46 or 47 or 48 or 52 or 53 or 54 or 88 or 89
91	remove duplicates from 90

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
CINAHL (EBSCO interface)	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform.	

Grey Literature

Dates for Search:	November 2018
Keywords:	Included terms for axicabtagene ciloleucel, lymphomas, chimeric antigen receptor T cell therapy
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- clinical trial registries
- regulatory agencies
- health economics
- clinical practice guidelines
- databases (free)
- Internet search
- open access journals.

Conferences and Meetings

American Society of Hematology (ASH)
http://www.hematology.org/

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

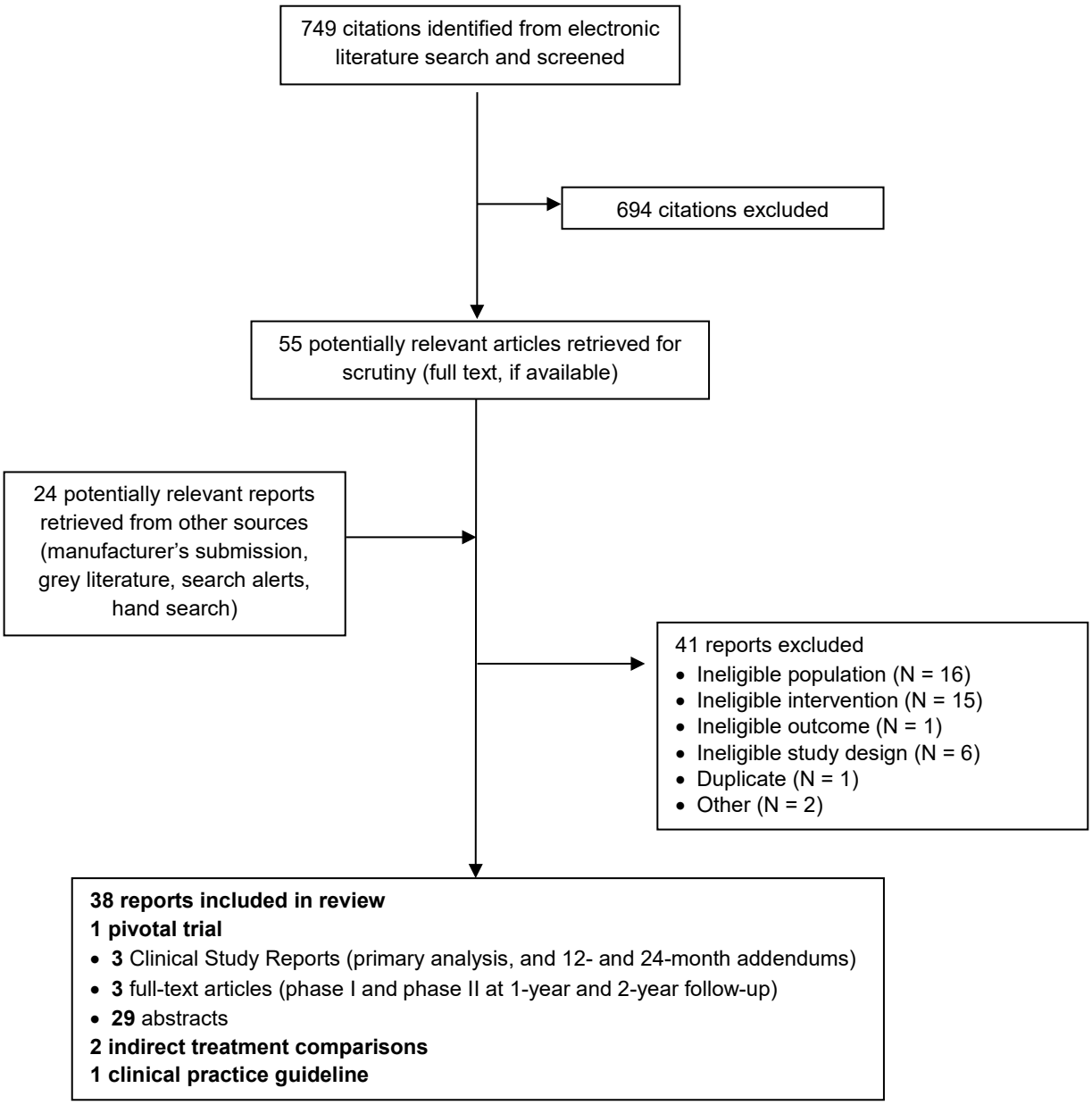
European Hematology Association (EHA)
https://ehaweb.org/

European Society for Medical Oncology (ESMO)
http://oncologypro.esmo.org/Meeting-Resources

Search: axicabtagene ciloleucel, Yescarta, axi-cel, KTE-C19, KTEC19, lymphomas, chimeric antigen receptor T cell therapy

Appendix 2: PRISMA Flow Diagram

Figure 5: Study Selection Flow Diagram for Clinical Review



Appendix 3: List of Included Studies

Pivotal Trial Clinical Study Reports (ZUMA-1)

1. Clinical study report: KTE-C19-101 a phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1) [CONFIDENTIAL manufacturer's submission]. Santa Monica (CA): Kite Pharma, Inc.; 2017 Jul 28.
2. Clinical study report addendum: 12-month follow-up analysis of ZUMA-1 cohorts 1 and 2. Addendum to module 5.3.5.1 ZUMA-1 clinical study report: KTE-C19-101 a phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1) [CONFIDENTIAL manufacturer's submission]. Santa Monica (CA): Kite Pharma, Inc.; 2018 Feb 9.
3. Clinical study report addendum: 24-month follow-up analysis of ZUMA-1 cohorts 1 and 2. Addendum to module 5.3.5.1 ZUMA-1 clinical study report: KTE-C19-101 a phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1) [CONFIDENTIAL manufacturer's submission]. Santa Monica (CA): Kite Pharma, Inc.; 2018 Nov 2.

Pivotal Trial Full-Text Articles (ZUMA-1)

1. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.
2. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 Anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. Mol Ther. 2017;25(1):285-295.
3. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1):31-42.

Pivotal Trial — Conference Abstracts (ZUMA-1)

1. Beaupierre A, Patterson A, Kahle N, et al. Interdisciplinary management of chemorefractory NHL patients treated with KTE-C19 (anti-CD19 CAR T cells) in phase 1 of the ZUMA-1 clinical study...Academy of Oncology Nurse & Patient Navigators, November 17-20, 2016, Las Vegas, Nevada. J Oncol Navig Surviv. 2016;7(9):56.
2. Ghobadi A, Locke FL, Neelapu SS, et al. Updated phase I results from ZUMA-1: a phase I-II multicenter study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in subjects with refractory aggressive non-Hodgkin lymphoma (NHL). Cancer Res. 2016;76(14 Suppl):CT135.
3. Gisselbrecht C, Locke FL, Bartlett NL, et al. A comparison of one year outcomes in patients with refractory large B cell lymphoma from ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1. Br J Haematol. 2018;181 (Suppl 1):72-73.
4. Lin Y, Locke FL, Neelapu SS, et al. Efficacy, safety, and covariates of outcomes with axicabtagene ciloleucel (axi-cel; KTE-C19) from ZUMA-1, a pivotal trial in patients with refractory, aggressive non-Hodgkin lymphoma (NHL). Hum Gene Ther. 2017;28 (12):A5.
5. Locke FL, Bartlett NL, Lekakis LJ, et al. Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma (NHL): long-term follow-up of ZUMA-1. Br J Haematol. 2018;181 (Suppl 1):25.
6. Locke FL, Ghobadi A, Jacobson CA, et al. Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma: durability of response in ZUMA-1. HemaSphere. 2018;2 (Suppl 2):83.
7. Locke FL, Ghobadi A, Jacobson CA, et al. Durability of response in patients with refractory large B cell lymphoma treated with axicabtagene ciloleucel in the pivotal phase 2 study, ZUMA-1. Clin Lymphoma Myeloma Leuk. 2018;18:S277-S278.
8. Locke FL, Ghobadi A, Jacobson CA, et al. Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (axi-cel) in patients (pts) with refractory large B cell lymphoma. J Clin Oncol. 2018;36(15 Suppl 1).
9. Locke FL, Ghobadi A, Lekakis LJ, et al. Axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma: outcomes by prior lines of therapy in ZUMA-1. HemaSphere. 2018;2 (Suppl 2):348.
10. Locke FL, Ghobadi A, Lekakis LJ, et al. Axicabtagene ciloleucel in patients with refractory large B cell lymphoma: outcomes by prior lines of therapy in the pivotal phase 2 study, ZUMA-1. Clin Lymphoma Myeloma Leuk. 2018;18:S276.

11. Locke FL, Ghobadi A, Lekakis LJ, et al. Outcomes by prior lines of therapy (LoT) in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (axi-cel) in patients (pts) with refractory large B cell lymphoma. J Clin Oncol. 2018;36(15 Suppl 1).

12. Locke FL, Neelapu SS, Bartlett NL, et al. Primary results from ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axicel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL). Cancer Res. 2017;77(13 Suppl 1).

13. Locke FL, Neelapu SS, Bartlett NL, et al. Clinical and biologic covariates of outcomes in ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL). Haematologica. 2017;102 (Suppl 2):172.

14. Locke FL, Neelapu SS, Bartlett NL, et al. Ongoing complete remissions in phase 1 of ZUMA-1: a phase 1-2 multi-center study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B cell non-Hodgkin lymphoma (NHL). Ann Oncol. 2016;27(Suppl 6).

15. Locke FL, Neelapu SS, Bartlett NL, et al. Updated phase 1 results from ZUMA-1: a phase 1-2 multi-center study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in subjects with refractory aggressive non-Hodgkin lymphoma (NHL). Mol Ther. 2016;1):S294.

16. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 clinical results of the ZUMA-1 (KTE-C19-101) study: a phase 1-2 multi-center study evaluating the safety and efficacy of anti-CD19 CAR T cells (KTE-C19) in subjects with refractory aggressive non-Hodgkin lymphoma (NHL). Blood. 2015;126(23):3991.

17. Lundry Locke F, Swarup Neelapu S, Bartlett NL, et al. Clinical and biologic covariates of outcomes in ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (r-NHL). J Clin Oncol. 2017;35(15 Suppl 1).

18. Neelapu S, Ghobadi A, Jacobson C, et al. Axicabtagene Ciloleucel (Axi-Cel) In Patients With Refractory Large B Cell Lymphoma: Long-Term Safety and Efficacy of ZUMA-1. Br J Haematol. 2019;185 (Suppl 1):26-27.

19. Neelapu S, Locke F, Bartlett N, et al. Ongoing complete remissions in ZUMA-1: a phase 1-2 multicenter study of KTE-C19 (Anti-CD19 CAR T cells) in patients with refractory aggressive B cell non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2016;16:S102.

20. Neelapu SS, Ghobadi A, Jacobson CA, et al. 2-year follow-up and high-risk subset analysis of ZUMA-1, the pivotal study of axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma. Blood. 2018;132(Suppl 1):2967.

21. Neelapu SS, Locke FL, Bartlett NL, et al. KTE-C19 (anti-CD19 CAR T cells) induces complete remissions in patients with refractory diffuse large B-cell lymphoma (DLBCL): results from the pivotal phase 2 ZUMA-1. Blood. 2016;128(22).

22. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphomas (NHL): primary results of the pivotal trial ZUMA-1. Hematol Oncol. 2017;35 (Suppl 2):28.

23. Neelapu SS, Locke FL, Bartlett NL, et al. A standardized comparison of outcomes in patients (pts) with refractory, aggressive non-Hodgkin Lymphoma (rNHL) from the SCHOLAR-1 analysis and the ZUMA-1 study of axicabtagene ciloleucel (axi-cel). Ann Oncol. 2017;28 (Suppl 5):v412.

24. Neelapu SS, Locke FL, Bartlett NL, et al. A comparison of one year outcomes in ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1 in patients with refractory, aggressive non-Hodgkin lymphoma (NHL). Blood. 2017;130(Suppl 1).

25. Neelapu SS, Locke FL, Bartlett NL, et al. Ongoing complete remissions (CR) in the phase 1 of ZUMA-1: a phase 1-2 multicenter study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in subjects with refractory aggressive B-cell non-Hodgkin lymphoma (NHL). J Clin Oncol. 2016;34(Suppl 15).

26. Neelapu SS, Locke FL, Bartlett NL, et al. A phase 2 multicenter trial of KTE-C19 (anti-CD19 CAR T cells) in patients with chemorefractory primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL): interim results from ZUMA-1. Blood. 2016;128(22).

27. Neelapu SS, Locke FL, Ghobadi A, et al. ZUMA-1 pivotal phase 2 trial of axicabtagene ciloleucel (axi-cel, KTE-C19; Anti-CD19 CAR T cells) in patients (pts) with refractory aggressive non-Hodgkin lymphoma (NHL). Mol Ther. 2017;25 (5 Suppl 1):333.

28. Rossi JM, Neelapu SS, Go WY, et al. Phase 1 biomarker analysis of the ZUMA-1 (KTE-C19-101) study: a phase 1-2 multi-center study evaluating the safety and efficacy of anti-CD19 CAR T cells (KTE-C19) in subjects with refractory aggressive non-Hodgkin lymphoma (NHL). Blood. 2015;126(23):2730.

29. Siddiqi T, Neelapu SS, Locke FL, et al. Updated results from ZUMA-1: a phase 1-2 multicenter study evaluating the safety and efficacy of KTE-C19 (anti-CD19 CAR T cells) in refractory aggressive B-cell non-Hodgkin lymphoma (NHL). Haematologica. 2016;101 (Suppl 1):318.

Indirect Treatment Comparisons

[redacted]

2. [redacted]

Clinical Practice Guideline

1. NCCN clinical practice guidelines in oncology (NCCN guidelines): B-cell lymphomas. Version 4.2018. Plymouth Meeting (PA): National Comprehensive Cancer Network, Inc.; 2018 May 15.

Appendix 4: List of Excluded Studies

Ineligible Population

1. Rossi JM, Galon J, Turcan S, et al. Characteristics of the pretreatment tumor microenvironment may influence clinical response in patients with refractory large B cell lymphoma treated with axicabtagene ciloleucel (axi-cel) in the pivotal ZUMA-1. Cancer Research Conference. 2018;78(13 Suppl 1).
2. Jaksic B, Pejsa V, Ostojic-Kolonic S, et al. Guidelines for diagnosis and treatment of chronic lymphocytic leukemia. Krohem B-CLL 2017. Acta Clin Croat. 2018;57(1):190-215.
3. Hoppe RT, Advani RH, Ai WZ, et al. NCCN guidelines insights Hodgkin lymphoma, version 1.2018 featured updates to the NCCN guidelines. JNCCN. 2018;16(3):245-254.
4. Pilichowska M, Pittaluga S, Ferry JA, et al. Clinicopathologic consensus study of gray zone lymphoma with features intermediate between DLBCL and classical HL. Blood Adv. 2017;1(26):2600-2609.
5. Rossi JM, Galon J, Turcan S, et al. Clinical response in ZUMA-1, the pivotal study of axicabtagene ciloleucel (axi-cel) in patients with refractory large B cell lymphoma, may be influenced by characteristics of the pretreatment tumor microenvironment (TME). Clin Lymphoma Myeloma Leuk. 2018;18:S281.

Ineligible Intervention

1. Locke FL, Neelapu SS, Bartlett NL, et al. Preliminary results of prophylactic tocilizumab after axicabtageneciloleucel (axi-cel; KTE-C19) treatment for patients with refractory, aggressive non-hodgkin lymphoma (NHL). Blood. 2017;130(Suppl 1).
2. Locke FL, Westin JR, Miklos DB, et al. Phase 1 results from ZUMA-6: Axicabtagene ciloleucel (axi-cel; kte-c19) in combination with atezolizumab for the treatment of patients with refractory diffuse large b cell lymphoma (DLBCL). Blood. 2017;130(Suppl 1).
3. Engert A, Balduini C, Brand A, et al. The European Hematology Association roadmap for European hematology research: a consensus document. Haematologica. 2016;101(2):115-208.
4. Zelenetz AD, Gordon LI, Wierda WG, et al. Diffuse large b-cell lymphoma version 1.2016: Clinical practice guidelines in oncology. JNCCN. 2016;14(2):196-231.
5. Lishner M, Avivi I, Apperley JF, et al. Hematologic malignancies in pregnancy: management guidelines from an international consensus meeting. J Clin Oncol. 2016;34(5):501-508.
6. Vitolo U, Seymour JF, Martelli M, et al. Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v91-v102.
7. Gonzalez-Barca E, Coronado M, Martin A, et al. Spanish Lymphoma Group (GELTAMO) guidelines for the diagnosis, staging, treatment, and follow-up of diffuse large B-cell lymphoma. Oncotarget. 2018;9(64):32383-32399.
8. Nair R, Kakroo A, Bapna A, et al. Management of Lymphomas: Consensus Document 2018 by an Indian Expert Group. Indian J Hematol Blood Transfus. 2018;34(3):398-421.
9. Hutchings M, Ladetto M, Buske C, et al. ESMO Consensus Conference on malignant lymphoma: management of 'ultra-high-risk' patients. Ann Oncol. 2018;29(8):1687-1700.
10. Miralles P, Navarro JT, Berenguer J, et al. GESIDA/PETHEMA recommendations on the diagnosis and treatment of lymphomas in patients infected by the human immunodeficiency virus. Med Clin (Barc). 2018;151(1):39.e31-39.e17.
11. Buske C, Hutchings M, Ladetto M, et al. ESMO Consensus Conference on malignant lymphoma: general perspectives and recommendations for the clinical management of the elderly patient with malignant lymphoma. Ann Oncol. 2018;29(3):544-562.
12. Boyiadzis M, Bishop MR, Abonour R, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of hematologic malignancies: multiple myeloma, lymphoma, and acute leukemia. J Immunother Cancer. 2016;4:90.
13. Doval DC, Bhurani D, Nair R, et al. Indian Council of Medical Research consensus document for the management of non-Hodgkin's lymphoma (high grade). Ind J Med Paediatr Oncol. 2017;38(1):51-58.
14. Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. Br J Haematol. 2016;174(1):43-56.

15. National Institute for Health and Care Excellence: clinical guidelines. Non-Hodgkin's lymphoma: diagnosis and management. London (GB): National Institute for Health and Care Excellence; 2016.

Ineligible Outcome

1. Neelapu SS, Locke FL, Bartlett NL, et al. Long-term follow-up ZUMA-1: a pivotal trial of axicabtagene ciloleucel (axi-cel; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL). Blood. 2017;130(Suppl 1).

Ineligible Study Design

1. Budde LE, Zaia JA. CD19 CAR-T therapy and sepsis: dancing with the devil. Blood. 2018;131(1):7-8.
2. Isaac D. CAR T-cell therapy shows high levels of durable response in refractory large B-cell lymphoma. J Clin Outcomes Manag. 2018;25(5).
3. Specht L, Aleman B, Eich H, et al. Recommendations for the clinical management of the elderly patient with malignant lymphoma. Ann Oncol. 2018;29(4):1069-1070.
4. Neelapu SS. An interim analysis of the ZUMA-1 study of KTE-C19 in refractory, aggressive non-Hodgkin lymphoma. Clin Adv Hematol Oncol. 2017;15(2):117-120.
5. Anonymous. DLBCL responds well to anti-CD19 CAR therapy. Cancer Discov. 2017;7(3):241-242.
6. Oluwole OO, Bishop MR, Gisselbrecht C, et al. Axicabtagene ciloleucel (axi-cel) versus standard-of-care therapy in patients with relapsed/refractory diffuse large B cell lymphoma: ZUMA-7, a phase 3, randomized study. Clin Lymphoma Myeloma Leuk. 2018;18:S293-S294.

Duplicate

1. National Institute for Health and Care Excellence: clinical guidelines. Non-Hodgkin's lymphoma: diagnosis and management. London (GB): National Institute for Health and Care Excellence; 2016.

Other

1. Anonymous. 2017 Annual Meeting of the American Society of Hematology, ASH 2017. Blood. 2017;130(Suppl 1).
2. Anonymous. 14th International Conference on Malignant Lymphoma Palazzo dei Congressi. Hematological Oncology Conference: 14th International Conference on Malignant Lymphoma Palazzo dei Congressi Switzerland. 2017;35(Suppl 2).

Studies Administering Axicabtagene Ciloleucel but Unclear Whether Patients Meet Approved Health Canada Indication (Conference Abstracts)

1. Byrne MT, Oluwole O, Allen D, et al. Commercial chimeric antigen receptor (CAR) T cells: unfamiliar roads and stalled cars. Biol Blood Marrow Transplant. 2019;25 (3 Suppl):S302.
2. Faramand R, Kotani H, Morrissey D, et al. Prediction of CAR T-related toxicities in R/R DLBCL patients treated with axicabtagene ciloleucel using point of care cytokine measurements. Biol Blood Marrow Transplant. 2019;25 (3 Suppl):S408-S409.
3. Jacobson CA, Hunter B, Armand P, et al. Axicabtagene ciloleucel in the real world: outcomes and predictors of response, resistance and toxicity. Blood. 2018;132(Suppl 1):92.
4. Jim HSL, Hoogland AI, Collier A, Booth-Jones M, Jain MD, Locke FL. Patient-reported and neurocognitive outcomes in patients treated with axicabtagene ciloleucel. Blood. 2018;132(Suppl 1):2289.
5. Lin Y, Locke FL, Neelapu SS, et al. Efficacy, safety, and covariates of outcomes with axicabtagene ciloleucel (axi-cel; KTE-C19) from ZUMA-1, a pivotal trial in patients with refractory, aggressive non-Hodgkin lymphoma (NHL). Hum Gene Ther. 2017;28 (12):A5.
6. Maakaron J, Penza S, El Boghdadly Z, et al. Procalcitonin as a potential biomarker for differentiating bacterial infectious fevers from cytokine release syndrome. Blood. 2018;132(Suppl 1):4216.
7. Nahas G, Komanduri KV, Pereira D, et al. Persistent cytopenias after chimeric antigen receptor T-cell immunotherapy for CD19+ aggressive lymphoma: a single institution experience. Biol Blood Marrow Transplant. 2019;25(3 Suppl):S180.
8. Nastoupil LJ, Jain MD, Spiegel JY, et al. Axicabtagene ciloleucel (axi-cel) CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: real world experience. Blood. 2018;132(Suppl 1):91.

9. Oak J, Spiegel JY, Sahaf B, et al. Target antigen downregulation and other mechanisms of failure after axicabtagene ciloleucel (CAR19) therapy. Blood. 2018;132(Suppl 1):4656.
10. Sano D, Nastoupil LJ, Fowler NH, et al. Safety of axicabtagene ciloleucel CD19 CAR T-cell therapy in elderly patients with relapsed or refractory large B-cell lymphoma. Blood. 2018;132(Suppl 1):96.
11. Spiegel JY, Sahaf B, Hossain N, et al. Elevated axicabtagene ciloleucel (CAR-19) expansion by immunophenotyping is associated with toxicity in diffuse large B-cell lymphoma. Blood. 2018;132(Suppl 1):576.

Appendix 5: Inclusion and Exclusion Criteria for the Pivotal Trial[37]

The inclusion criteria for ZUMA-1 were the following:[18,37]

1. Histologically confirmed aggressive B-cell non-Hodgkin lymphoma, including the following types defined by the World Health Organization 2008 criteria:
   - diffuse large B-cell lymphoma (DLBCL) not otherwise specified, T-cell/histiocyte rich large B-cell lymphoma, DLBCL associated with chronic inflammation, Epstein-Barr virus + DLBCL of the elderly
   - primary mediastinal (thymic) large B-cell lymphoma
   - transformation of follicular lymphoma to DLBCL.
2. Chemotherapy-refractory disease, defined as one or more of the following:
   - no response to first-line therapy (primary refractory disease), defined as progressive disease as best response to first-line therapy or stable disease (SD) as best response after at least four cycles of first-line therapy (e.g., four cycles of R-CHOP, which is rituximab, cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], and prednisone) with SD duration no longer than six months from last dose of therapy; patients who were intolerant to first-line therapy chemotherapy were excluded
   - no response to second or greater lines of therapy, defined as progressive disease as best response to most recent therapy regimen or SD as best response after at least two cycles of last line of therapy with SD duration no longer than six months from last dose of therapy
   - refractory after autologous stem cell transplant (SCT), defined as occurrence of disease progression or relapse ≤ 12 months after autologous SCT (must have biopsy proven recurrence in relapsed patients) or, if salvage therapy was given after autologous SCT, the patient must have had no response to or relapsed after the last line of therapy.
3. Received adequate prior therapy, including, at a minimum:
   - anti-CD20 monoclonal antibody unless investigator determines that tumour is CD20 negative
   - an anthracycline-containing chemotherapy regimen
   - for patients with transformed follicular lymphoma, must have received prior chemotherapy for follicular lymphoma and subsequently have chemo-refractory disease after transformation to DLBCL.
4. Measurable disease according to the International Working Group's revised response criteria for malignant lymphoma. Lesions that had been previously irradiated were considered measurable only if progression had been documented following completion of radiation therapy.
5. No evidence of central nervous system (CNS) lymphoma (MRI of brain).
6. At least two weeks or five half-lives, whichever is shorter, must have elapsed since any prior systemic therapy at the time leukapheresis was planned for the patient, except for systemic inhibitory/stimulatory immune checkpoint therapy. At least three half-lives must have elapsed from any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy at the time leukapheresis was planned for the patient (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc).
7. Toxicities due to prior therapy must be stable and recovered to ≤ grade 1 (except for clinically non-significant toxicities such as alopecia).
8. Age 18 or older.
9. ECOG performance status of zero or one.
10. Absolute neutrophil count ≥ 1,000/μL.
11. Platelet count ≥ 75,000/μL.
12. Absolute lymphocyte count ≥ 100/μL.

13. Adequate hematologic, renal, hepatic, pulmonary, and cardiac function, defined as:
    - creatinine clearance (as estimated by Cockcroft Gault) ≥ 60 mL/min
    - serum aspartate transaminase/alanine transaminase ≤ 2.5 upper limit of normal
    - total bilirubin ≤ 1.5 mg/dL, except in patients with Gilbert's syndrome
    - cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram, and no clinically significant ECG findings
    - no clinically significant pleural effusion
    - baseline oxygen saturation > 92% on room air.
14. Females of child-bearing potential must have a negative serum or urine pregnancy test.

The exclusion criteria for ZUMA-1 were: [18,37]

1. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g., cervix, bladder, breast) or follicular lymphoma unless disease free for at least three years.
2. History of Richter's transformation of chronic lymphocytic leukemia.
3. ASCT within six weeks of planned axicabtagene ciloleucel infusion.
4. History of allogeneic stem cell transplant.
5. Prior CD19 targeted therapy with the exception of patients who received axicabtagene ciloleucel in this study and are eligible for re-treatment.
6. Prior chimeric antigen receptor therapy or other genetically modified T-cell therapy.
7. History of severe, immediate hypersensitivity reaction attributed to aminoglycosides.
8. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with the Kite Medical Monitor.
9. Known history of infection with HIV or hepatitis B (HBsAg positive) or hepatitis C virus (anti-hepatitis C virus positive); however, a history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per quantitative polymerase chain reaction and/or nucleic acid testing.
10. Presence of any indwelling line or drain (e.g., percutaneous nephrostomy tube, indwelling Foley catheter, biliary drain, or pleural/peritoneal/pericardial catheter); however, dedicated central venous access catheters such as a Port-a-Cath or Hickman catheter are permitted.
11. Patients with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma, cerebrospinal fluid malignant cells, or brain metastases.
12. History or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement.
13. Patients with cardiac atrial or cardiac ventricular lymphoma involvement.
14. History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, or other clinically significant cardiac disease within 12 months of enrolment.
15. Requirement for urgent therapy due to tumour mass effects such as bowel obstruction or blood vessel compression.
16. Primary immunodeficiency.
17. History of deep vein thrombosis or pulmonary embolism within six months of enrolment.
18. Any medical condition likely to interfere with assessment of safety or efficacy of study treatment.
19. History of severe immediate hypersensitivity reaction to any of the agents used in this study.
20. Live vaccine ≤ six weeks prior to planned start of conditioning regimen.

21. Women of child-bearing potential who were pregnant or breastfeeding, due to the potentially dangerous effects of the preparative chemotherapy on the fetus or infant.
22. Patients of both genders who were not willing to practice birth control from the time of consent through six months after the completion of axicabtagene ciloleucel.
23. A patient who, in the investigators' judgment, is unlikely to complete all protocol-required study visits or procedures, including follow-up visits, or comply with the study requirements for participation.
24. History of autoimmune disease (e.g., Crohn disease, rheumatoid arthritis, systemic lupus) resulting in end organ injury or requiring systemic immunosuppression/ systemic disease modifying agents within the last two years.

Appendix 6: Additional Definitions

Table 32: Definitions of Disease Response Categories

Outcome and Characteristics	Details
CR	
Definition	Proportion of patients with complete disappearance of all detectable clinical evidence of disease and disease-related symptoms, if present before therapy
Method of assessment	Assessed by the study investigators and via IRC according to the IWG 2007 response criteria
Unit of measurement	Proportion
Other details	All who did not meet the criteria for CR (or PR) by the analysis data cut-off date were considered non-responders. The terms “complete response” and “complete remission” were used interchangeably.
PR	
Definition	Proportion of patients with regression of measurable disease and no new sites[69]
Method of assessment	Assessed by the study investigators and via IRC according to the IWG 2007 response criteria
Unit of measurement	Proportion
Other details	All who did not meet the criteria for PR (or CR) by the analysis data cut-off date were considered non-responders. The terms “partial response” and “partial remission” were used interchangeably.
SD	
Definition	Proportion of patients with neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Method of assessment	Assessed by the study investigators and via IRC according to the IWG 2007 response criteria
Unit of measurement	Proportion
PD	
Definition	Proportion of patients with appearance of any new lesion or increase by ≥ 50% of previously involved sites from nadir[69]
Method of assessment	Assessed by the study investigators and via IRC according to the IWG 2007 response criteria
Unit of measurement	Proportion

CR = complete response or complete remission; IRC = Independent Central Review Committee; IWG = International Working Group; PD = progressive disease; PR = partial response or partial remission; SD = stable disease.

Table 33: Definitions of Notable Harms

Outcome and Characteristics	Details
CRS	
Definition	CRS is a symptom complex associated with the use of monoclonal antibodies and adoptive cell therapies that activate lymphocytes, and that results from the release of cytokines from cells targeted by antibodies, immune effector cells recruited to the tumour area, and the patient’s immune cells activated during this process. CRS is induced by the activated anti-CD19 CAR T cells upon engagement with the CD19 target; therefore, all reported events of CRS were considered to be related to axicabtagene ciloleucel. Clinical signs and symptoms include: • cardiac • gastrointestinal

Outcome and Characteristics	Details
	• laboratory (coagulation, renal, and hepatic) • respiratory • skin • vascular (hypotension) • constitutional (fever, rigors, headaches, malaise, fatigue, arthralgia, nausea, and vomiting).
Measurement method	Identified via collection of the symptoms on a case report form specifically designed to collect CRS. Specific symptoms of the CRS were collected on the AE log and were linked to the CRS syndrome. CRS syndrome severity was graded according to a modification of the grading system proposed by Lee et al. In the modified grading scale, neurologic AEs were not reported as part of the CRS syndrome; rather, they were reported on the AE log separately based on specific symptoms per CTCAE v4.03. **Grading Scale**[94] **Grade 1**: Symptoms are not life threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise). **Grade 2**: Symptoms require and respond to moderate intervention; oxygen requirement < 40%, hypotension responsive to fluids or low dose of 1 vasopressor, or grade 2 organ toxicity. **Grade 3**: Symptoms require and respond to aggressive intervention; oxygen requirement ≥ 40%, hypotension requiring high dose or multiple vasopressors, or grade 3 organ toxicity or grade 4 transaminitis. **Grade 4:** Life-threatening symptoms; requirements for ventilator support, or grade 4 organ toxicity (excluding transaminitis). **Grade 5:** Death
Other details	Collected for 24 months or until disease progression (whichever occurred first)
Neurological Event	
Definition	Neurotoxicity (e.g., encephalopathy, somnolence, aphasia)
Measurement method	Neurological exam, including additional workup as clinically indicated (e.g., brain MRI, evaluation of CSF, EEG) Search strategy (of case report forms) based on known neurologic toxicities associated with anti-CD19 immunotherapy. The search strategy focused on CNS toxicity, without regard to temporal relationship or concomitant conditions (e.g., CRS). Events were identified with a pre-specified search list of MedDRA preferred terms. Additionally, the MedDRA system organ classes of psychiatric disorders and nervous system disorders were reviewed for additional events. These events were then evaluated for potential inclusion as neurologic AEs. **Grading Assessment** (CTCAE v4.03) Grade 1 examples: • somnolence — mild drowsiness or sleepiness • confusion — mild disorientation • encephalopathy — mild limiting of ADL • dysphasia — not impairing ability to communicate • brief partial seizure, no loss of consciousness Grade 2 examples: • somnolence — moderate, limiting instrumental ADL • confusion — moderate disorientation, limiting instrumental ADL • encephalopathy — limiting instrumental ADL • dysphasia — moderate, impairing ability to communicate spontaneously

Outcome and Characteristics	Details
	• brief generalized seizure Grade 3 examples: • somnolence — obtundation or stupor • confusion — severe disorientation, limiting self-care ADL • encephalopathy — limiting self-care ADL • dysphasia — severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly • multiple seizures despite medical intervention • weakness limiting self-care ADL, disabling • complete bowel/bladder incontinence Grade 4 examples: • life-threatening consequences • urgent intervention indicated • mechanical ventilation • life threatening; prolonged repetitive seizures
Other details	Collected for 24 months or until disease progression (whichever occurred first)
Cytopenia	
Definition	NR
Measurement method	Analysis of individual cytopenias was conducted using the SMQ hematopoietic thrombocytopenia (narrow) for thrombocytopenias, the SMQ hematopoietic erythropenia (broad) for anemias, and the following preferred terms for neutropenias: febrile neutropenia, neutropenia, and neutrophil count decreased. Prolonged cytopenias were defined as follows: • any grade 3 or higher cytopenias with duration ≥ 30 days • any consecutive events of grade 3 cytopenias with combined duration ≥ 30 days. Post-baseline CTCAE grade 3 or grade 4 laboratory toxicities for neutrophil decreased, lymphocyte decreased, hemoglobin decreased, and platelet decreased were analyzed separately.
Other details	Collected for 24 months or until disease progression (whichever occurred first)
Infection	
Definition	NR

Measurement method	Infections that occurred after treatment with anti-CD19 CAR T cells were identified using the following MedDRA HLGT within the MedDRA system organ class of infections and infestations:
	• bacterial infections encompassed preferred terms within the following MedDRA HLGTs
	  ○ bacterial infectious disorders
	  ○ chlamydial infectious disorders (separate HLGT from other bacterial infections)
	• viral infections encompassed preferred terms within the MedDRA HLGT of viral infectious disorders
	• opportunistic infections encompassed preferred terms within the following MedDRA HLGTs
	  ○ fungal infectious disorders
	  ○ mycobacterial infectious disorders (separate HLGT from other bacterial infections)
	• other infections encompassed preferred terms within the MedDRA HLGT of infections — pathogen unspecified.

Other details	Collected for 24 months or until disease progression (whichever occurred first)
B-Cell Aplasia	
Definition	Undetectable B cells; B-cell count < 61 B cells/μL (Kochenderfer, 2012)

Outcome and Characteristics	Details
Measurement method	Flow cytometry
Other details	Incidence of recovery was assessed for each patient with available samples at the following time points: prior to conditioning chemotherapy and at month 3, month 6, month 9, month 12, month 15, month 18, and month 24. Severity grading was not conducted, as an accepted scale does not exist. The incidence of hypogammaglobulinemia was assessed both by the MedDRA preferred term and by a search of immunoglobulin usage. Collected for 24 months or until disease progression (whichever occurred first)
Secondary Malignancy	
Definition	NR
Measurement method	Identified via collection on a case report form in which the investigator classified the event as a secondary malignancy, or as an abnormal expansion and persistence. Additionally, AEs that were coded into the system organ class of neoplasms as benign, malignant, and unspecified (including cysts and polyps), with the exception of preferred terms containing “B-cell” and “lymphoma,” were reviewed to identify other potential events.
Other details	Collected for 24 months or until disease progression (whichever occurred first)

ADL = activities of daily living; AE = adverse event; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CTCAE = *Common Terminology Criteria for Adverse Events*; EEG = electroencephalogram; HLGT = high-level group terms; MedDRA = *Medical Dictionary for Regulatory Activities*; MRI = magnetic resonance imaging; NR = not reported; SMQ = standard MedDRA query.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off; Study Protocol, August 12, 2016, amendment).[32]

Appendix 7: Additional Data for Main Analysis

Table 34: Summary of Concordance Between Independent Central Review Committee and Investigator Assessment of Objective Response (Modified Intention-to-Treat)

	Primary Analysis[a]			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Sample size, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	101
Concordant Assessments, n (%)						
Responder according to both IRC and investigator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nonresponder according to both IRC and investigator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discordant Assessments, n (%)						
Responder according to IRC; *nonresponder* according to investigator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nonresponder according to IRC; *responder* according to investigator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Summary Measures of Concordance						
Overall concordance [b]	[redacted]	[redacted]	77.2	[redacted]	[redacted]	81.2
Kappa coefficient (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.45 (0.24 to 0.65)

CI = confidence interval; CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; IRC = Independent Central Review Committee; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Note: Disease status was assessed by the IRC and by the investigator per Cheson et al. 2007 for the modified intention-to-treat data set (i.e., all patients who were treated with at least 1.0 x 10^6 anti-CD19 CAR T cells/kg).[69] "Responders" include those with either a complete response or partial response; "non-responders" includes all others (i.e., stable disease, progressive disease, assessment not done).

[a] The IRC's assessment of disease was approximately six weeks earlier than the clinical data cut-off date for the primary analysis.

[b] Overall concordance is the percentage of patients whose disease assessments according to the IRC and the investigator match.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off).[32] For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off),[32,34] Locke et al. 2019,[37] and Locke et al. 2018.[41]

Table 35: Ongoing Response (Independent Central Review Committee)

	Primary Analysis[a]			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Ongoing Response						
Number of patients who could be evaluated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	101
Number of patients with ongoing responses (CR or PR) at cut-off date, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36 (36)
Number of patients with ongoing CR at cut-off date, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35 (35)
Number of patients with ongoing PR at cut-off date, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1 (1)

CR = complete response; CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; NR = not reported; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response; TFL = transformed follicular lymphoma.

[a] The Independent Central Review Committee's assessment of disease was approximately 6 weeks earlier than the clinical data cut-off date for the primary analysis.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017 data cut-off).[32] For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Table 36: Secondary Clinical Effectiveness Outcomes (Independent Central Review Committee) (Modified Intention-to-Treat)

	Primary Analysis[a]			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
DOR[b]						
Number of patients with response (CR or PR) by cut-off date	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DOR (CR or PR) time, KM median (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NE (10.9 to NE)
Type of Events (Resulting in End of Response)						
Disease progression, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease- or treatment-related death, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censoring Reason						
Response ongoing (CR or PR) at cut-off date, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	36

	Primary Analysis[a]			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Started new anticancer therapy, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axicabtagene ciloleucel re-treatment before progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allogeneic SCT while in response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients in response (KM estimate) at 3 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients in response (KM estimate) at 6 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients in response (KM estimate) at 12 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients in response (KM estimate) at 24 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS[c]						
Number of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS time, KM median (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of Events (Resulting in End of PFS)						
Disease progression, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease- or treatment-related death, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censoring Reason						
Response ongoing, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Started new anticancer therapy, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response not yet assessed, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axicabtagene ciloleucel re-treatment before progressive disease, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allogeneic SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Primary Analysis[a]			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
	[redacted]					
Percentage of patients (KM estimate) with PFS at 3 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients (KM estimate) with PFS at 6 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients (KM estimate) with PFS at 9 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients (KM estimate) with PFS at 12 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients (KM estimate) with PFS at 24 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CR = complete response; CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; KM = Kaplan–Meier; NA = not applicable; NE = not estimable; NR = not reported; PFS = progression-free survival; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

[a] The Independent Central Review Committee's assessment of disease was approximately six weeks earlier than the clinical data cut-off date for the primary analysis.

[b] DOR was defined only for patients with objective response and was the time from the first objective response to disease progression or to death due to disease relapse or drug-related toxicity. In the primary analysis, DOR was censored for ongoing response or start of new anticancer therapy (*excluding* SCT). In the 24-month analysis, DOR was censored for ongoing response, the start of new anticancer therapy (*including* SCT received while in response), or re-treatment with axicabtagene ciloleucel received before progression of disease.

[c] PFS was defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression or death from any cause. In the primary analysis, PFS was censored for ongoing response, the start of new anticancer therapy (*excluding* SCT), or response not yet assessed. In the 24-month analysis, PFS was censored for ongoing response, the start of new anticancer therapy (*including* SCT), or re-treatment received before progression of disease.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off)[32] and Neelapu et al. 2017.[35] For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Table 37: Subgroup Analysis of Progression-Free Survival Rate (Independent Central Review Committee) (Modified Intention-to-Treat)

	Primary Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	101	
Subgroup	**n/N[a]**	**PFS Rate (95% CI)[b]**
Overall	[redacted]	[redacted]
Number of prior chemotherapies		
1	[redacted]	[redacted]
2 to 3	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]
Type of lymphoma		
DLBCL	[redacted]	[redacted]
PMBCL	[redacted]	[redacted]
TFL	[redacted]	[redacted]
Age at baseline		
< 65 years	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]
Sex		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Race		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
ECOG performance status		
Score of 0	[redacted]	[redacted]
Score of 1	[redacted]	[redacted]
Refractory to first-line therapy		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Refractory to ≥ 2 consecutive lines of therapy		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Relapsed/refractory status		
Primary refractory	[redacted]	[redacted]
Refractory to ≥ second-line therapy	[redacted]	[redacted]
Relapsed post-autologous SCT	[redacted]	[redacted]
Tumour burden per IRC at the time of therapy		
≤ median	[redacted]	[redacted]
> median	[redacted]	[redacted]
Stage of disease		

	Primary Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	101	
Subgroup	**n/N[a]**	**PFS Rate (95% CI)[b]**
I to II	[redacted]	[redacted]
III to IV	[redacted]	[redacted]
CD19 at baseline (histological score)		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Lymphoma subtype[c]		
HGBCL (triple or double hit, HGBCL, NOS)	[redacted]	[redacted]
MYC, BCL2, co-expressor by IHC	[redacted]	[redacted]

BCL = B-cell lymphoma; CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; HGBCL = high-grade B-cell lymphoma; IHC = immunohistochemistry; IRC = Independent Central Review Committee; NE = not estimable; NOS = not otherwise specified; PFS = progression-free survival; PMBCL = primary mediastinal large B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

[redacted]

Source: Information submitted by manufacturer (manufacturer response, February 1, 2019; data cut-off not reported).[79]

Table 38: Subgroup Analysis of Overall Survival Rate (Modified Intention-to-Treat)

	24-Month Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	101	
Subgroup	**n/N [a]**	**OS Rate (95% CI)**
Overall	[redacted]	[redacted]
Number of prior chemotherapies		
1	[redacted]	[redacted]
2 to 3	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]
Type of lymphoma		
DLBCL	[redacted]	[redacted]
PMBCL	[redacted]	[redacted]
TFL	[redacted]	[redacted]
Age at baseline		
< 65 years	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]
Sex		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]

	24-Month Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	**101**	
Subgroup	**n/N [a]**	**OS Rate (95% CI)**
Race		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
ECOG performance status		
Score of 0	[redacted]	[redacted]
Score of 1	[redacted]	[redacted]
Refractory to first-line therapy		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Refractory to ≥ 2 consecutive lines of therapy		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Relapsed/refractory status		
Primary refractory	[redacted]	[redacted]
Refractory to ≥ second-line therapy	[redacted]	[redacted]
Relapsed to ≥ second-line therapy	[redacted]	[redacted]
Relapsed post-autologous SCT	[redacted]	[redacted]
Tumour burden at the time of therapy		
≤ median	[redacted]	[redacted]
> median	[redacted]	[redacted]
Stage of disease		
I to II	[redacted]	[redacted]
III to IV	[redacted]	[redacted]
CD19 at baseline (histological score)		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]

CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; KM = Kaplan–Meier; OS = overall survival; PMBCL = primary mediastinal B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

Note: OS rate was estimated per Kaplan–Meier method. 95% CIs are the upper and lower 95% confidence limits of OS rate KM estimates.

[a] n/N signifies the number (n) of patients at risk out of the total number (N) evaluable for a given subgroup. N does not total to 101 for all subgroups because not all characteristics were evaluable for each patient.

Source: Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off).[37]

Table 39: Detailed Summary of Specific Treatment-Emergent Adverse Events (Safety Analysis Set)

	Primary Analysis				24-Month Analysis			
	Phase I and Phase II				Phase I and Phase II			
Sample size, N	108				108			
Most common AEs[a], n (%)	**All Grades**	**Grade 3**	**Grade 4**	**Grade 5**	**All Grades**	**Grade 3**	**Grade 4**	**Grade 5**
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	94 (87)	15 (14)	0 (0)	0 (0)
Anemia	[redacted]	[redacted]	[redacted]	[redacted]	73 (68)	46 (43)	3 (3)	0 (0)
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	63 (58)	14 (13)	1 (1)	0 (0)
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	63 (58)	0 (0)	0 (0)	0 (0)
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	57 (53)	3 (3)	0 (0)	0 (0)
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	55 (51)	2 (2)	0 (0)	0 (0)
Headache	[redacted]	[redacted]	[redacted]	[redacted]	50 (46)	1 (1)	0 (0)	0 (0)
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	48 (44)	5 (5)	0 (0)	0 (0)
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	48 (44)	10 (9)	32 (30)	0 (0)
Hypoalbuminemia	[redacted]	[redacted]	[redacted]	[redacted]	43 (40)	1 (1)	0 (0)	0 (0)
Hypocalcemia	[redacted]	[redacted]	[redacted]	[redacted]	43 (40)	7 (6)	0 (0)	0 (0)
Tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	43 (40)	2 (2)	0 (0)	0 (0)
Chills	[redacted]	[redacted]	[redacted]	[redacted]	40 (37)	0 (0)	0 (0)	0 (0)
Encephalopathy	[redacted]	[redacted]	[redacted]	[redacted]	40 (37)	23 (21)	2 (2)	0 (0)
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	39 (36)	33 (31)	2 (2)	0 (0)
Hyponatremia	[redacted]	[redacted]	[redacted]	[redacted]	38 (35)	12 (11)	0 (0)	0 (0)
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]	38 (35)	11 (10)	15 (14)	0 (0)
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	37 (34)	1 (1)	0 (0)	0 (0)
Hypokalemia	[redacted]	[redacted]	[redacted]	[redacted]	36 (33)	3 (3)	0 (0)	0 (0)
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	36 (33)	7 (6)	28 (26)	0 (0)
Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]	34 (31)	11 (10)	1 (1)	0 (0)
Tremor	[redacted]	[redacted]	[redacted]	[redacted]	33 (31)	2 (2)	0 (0)	0 (0)
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]	33 (31)	3 (3)	28 (26)	0 (0)
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	32 (30)	0 (0)	0 (0)	0 (0)
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]	32 (30)	8 (7)	9 (8)	0 (0)
Cough	[redacted]	[redacted]	[redacted]	[redacted]	31 (29)	0 (0)	0 (0)	0 (0)
Hypophosphatemia	[redacted]	[redacted]	[redacted]	[redacted]	31 (29)	18 (17)	2 (2)	0 (0)
Confusional state	[redacted]	[redacted]	[redacted]	[redacted]	29 (27)	10 (9)	0 (0)	0 (0)
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	23 (21)	0 (0)	0 (0)	0 (0)
Dyspnea	[redacted]	[redacted]	[redacted]	[redacted]	23 (21)	2 (2)	0 (0)	0 (0)
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	22 (20)	5 (5)	1 (1)	0 (0)
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]	[redacted]	22 (20)	2 (2)	20 (19)	0 (0)

	Primary Analysis				24-Month Analysis			
	Phase I and Phase II				Phase I and Phase II			
Sample size, N	108				108			
Most common AEs[a], n (%)	**All Grades**	**Grade 3**	**Grade 4**	**Grade 5**	**All Grades**	**Grade 3**	**Grade 4**	**Grade 5**
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	21 (19)	0 (0)	0 (0)	0 (0)
Sinus tachycardia	[redacted]	[redacted]	[redacted]	[redacted]	21 (19)	0 (0)	0 (0)	0 (0)
Hyperglycemia	[redacted]	[redacted]	[redacted]	[redacted]	20 (19)	5 (5)	0 (0)	0 (0)
Hypomagnesemia	[redacted]	[redacted]	[redacted]	[redacted]	20 (19)	0 (0)	0 (0)	0 (0)
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]	20 (19)	5 (5)	13 (12)	0 (0)
Aphasia	[redacted]	[redacted]	[redacted]	[redacted]	19 (18)	8 (7)	0 (0)	0 (0)
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]	19 (18)	7 (6)	0 (0)	0 (0)
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]	18 (17)	8 (7)	1 (1)	0 (0)
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	17 (16)	8 (7)	0 (0)	0 (0)
Muscular weakness	[redacted]	[redacted]	[redacted]	[redacted]	17 (16)	1 (1)	0 (0)	0 (0)
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]	17 (16)	2 (2)	0 (0)	0 (0)
Weight decreased	[redacted]	[redacted]	[redacted]	[redacted]	17 (16)	0 (0)	0 (0)	0 (0)
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	16 (15)	2 (2)	0 (0)	0 (0)
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	16 (15)	1 (1)	0 (0)	0 (0)
Hypogammaglobulinemia	[redacted]	[redacted]	[redacted]	[redacted]	16 (15)	0 (0)	0 (0)	0 (0)
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	16 (15)	1 (1)	0 (0)	0 (0)
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	15 (14)	1 (1)	0 (0)	0 (0)
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]	13 (12)	3 (3)	0 (0)	0 (0)
Dry mouth	[redacted]	[redacted]	[redacted]	[redacted]	13 (12)	0 (0)	0 (0)	0 (0)
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	13 (12)	0 (0)	0 (0)	0 (0)
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	13 (12)	0 (0)	0 (0)	0 (0)
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	11 (10)	0 (0)	0 (0)	0 (0)

AE = adverse event; CSR = Clinical Study Report.

[a] Frequency of AE of any severity occurring in ≥ 10% of patients in phase I and phase II combined. Notable harms (i.e., cytokine release syndrome, infections, cytopenias, and neurological events) occurring in ≥ 5% are listed in the notable AEs section.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off).[32] For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Appendix 8: Additional Data by Investigator Assessment of Disease

Table 40: Primary Efficacy Outcome, Objective Response Rate (Investigator Assessment) (Modified Intention-to-Treat)

	Primary Analysis			Primary Analysis, All Patients			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Sample size, N	72	20	92	77	24	101	77	24	101
ORR (CR + PR), n % (95% CI)[a]	58 81 [redacted]	17 85 [redacted]	75 82 (72 to 89)	63 82 [redacted]	20 83 [redacted]	83 82 (73 to 89)	[redacted]	[redacted]	84 83 ([redacted]
P-value of exact test of ORR ≤ 20%	[redacted]	[redacted]	< 0.0001[b]	[redacted][c]	[redacted]	[redacted][c]	[redacted][c]	[redacted]	< 0.0001[c]
Time to response (CR or PR), median (range), months[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.0 (0.8 to 6.0)	[redacted]	[redacted]	1.0 [redacted] (IQR 1,1)
Breakdown of Best ORR									
CR, n % (95% CI)[a]	34 47 ([redacted]	14 70 [redacted]	48 52 [redacted]	38 49 [redacted]	17 71 [redacted]	55 54 [redacted]	[redacted]	[redacted]	59 58 [redacted]
PR, n % (95% CI)[a]	24 33 [redacted]	3 15 [redacted]	27 29 [redacted]	25 32 [redacted]	3 13 [redacted]	28 28 [redacted]	[redacted]	[redacted]	25 25 [redacted]
SD, n % (95% CI)[a]	9 13 ([redacted]	2 10 ([redacted]	11 12 [redacted]	9 12 [redacted]	2 8 [redacted]	11 11 [redacted]	[redacted]	[redacted]	10 10 [redacted]
PD, n % (95% CI)[a]	[redacted]	[redacted]	[redacted]	4 5 [redacted]	1 4 [redacted]	5 5 [redacted]	[redacted]	[redacted]	5 5 [redacted]

	Primary Analysis			Primary Analysis, All Patients			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Death before the first disease assessment, n % (95% CI) [a]				1 1 	1 4 	2 2 			2 2 

CI = confidence interval; CR = complete response; CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; IQR = interquartile range; mITT = modified intention-to-treat; ORR = objective response rate; PD = progressive disease; PR = partial response; PMBCL = primary mediastinal large B-cell lymphoma; SD = stable disease; TFL = transformed follicular lymphoma.

Note: Disease status used was the investigator assessment of disease status per Cheson et al. 2007 for the mITT data set.[69] Primary analysis was conducted when 72 patients in the mITT set of cohort I and 20 patients in the mITT set of cohort II had had the opportunity to be assessed for response at the six-month disease assessment. At the primary analysis data cut-off date (January 27, 2017), an additional nine patients had been enrolled but had not yet had an opportunity to be followed for a full six months; these patients are included in the "Primary Analysis, All Patients" column.

[a] 95% CIs determined using the Clopper–Pearson method.

[b] The ORR for cohort I and cohort II combined was tested at a one-sided alpha level of 0.0075 for the first 92 patients.

[c] The type I error rate was not adjusted for multiple testing in this analysis.

[d] Time to response was only evaluated in those patients who achieved an objective response (CR or PR); sample size was based on the number with ORR. Time-to-first-objective-response was calculated as (date of first observed PR or CR – axicabtagene ciloleucel infusion date + 1)/(365.25/12).

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off)[32] and Neelapu et al. 2017.[35] For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Table 41: Subgroup Analysis of Objective Response Rate (Investigator Assessment) (Modified Intention-to-Treat)

	Primary Analysis		24-Month Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)		Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	**101**		[redacted]	
Subgroup	**n/N[a]**	**ORR (95% CI)[b]**	**n/N[a]**	**ORR (95% CI)[b]**
Overall	83/101	0.82 (0.73 to 0.89)	[redacted]	[redacted]
Number of prior chemotherapies				
1	[redacted]	[redacted]	[redacted]	[redacted]
2 to 3	[redacted]	[redacted]	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]	[redacted]	[redacted]
Type of lymphoma				
DLBCL	[redacted]	[redacted]	[redacted]	[redacted]
PMBCL	[redacted]	[redacted]	[redacted]	[redacted]
TFL	[redacted]	[redacted]	[redacted]	[redacted]
Cell of origin				
Germinal center B-cell–like subtype	43/49	0.88 (0.75 to 0.95)	[redacted]	[redacted]
Activated B-cell–like subtype	13/17	0.76 (0.50 to 0.83)	[redacted]	[redacted]
Age at baseline				
< 65 years	61/77	0.79 (0.68 to 0.88)	[redacted]	[redacted]
≥ 65 years	22/24	0.92 (0.73 to 0.99)	[redacted]	[redacted]
Sex				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Race				
White	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status				
Score of 0	[redacted]	[redacted]	[redacted]	[redacted]

	Primary Analysis		24-Month Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)		Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	**101**		[redacted]	
Subgroup	**n/N[a]**	**ORR (95% CI)[b]**	**n/N[a]**	**ORR (95% CI)[b]**
Score of 1	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to first-line therapy				
Yes	23/26	0.88 (0.70 to 0.98)	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to ≥ 2 consecutive lines of therapy				
Yes	42/54	0.78 (0.64 to 0.88)	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Relapsed/refractory status				
Primary refractory	[redacted]	[redacted]	[redacted]	[redacted]
Refractory to ≥ second-line therapy	65/78	0.83 (0.73 to 0.91)	[redacted]	[redacted]
Relapsed to ≥ second-line therapy			[redacted]	[redacted]
Relapsed post-autologous SCT	16/21	0.76 (0.53 to 0.92)	[redacted]	[redacted]
Tumour burden at the time of therapy				
≤ median	[redacted]	[redacted]	[redacted]	[redacted]
> median	[redacted]	[redacted]	[redacted]	[redacted]
Stage of disease				
I to II	13/15	0.87 (0.60 to 0.98)	[redacted]	[redacted]
III to IV	70/86	0.81 (0.72 to 0.89)	[redacted]	[redacted]
CD19 at baseline (histological score)				
Positive	63/74	0.85 (0.75 to 0.92)	[redacted]	[redacted]
Negative	6/8	0.75 (0.35 to 0.97)	[redacted]	[redacted]
CD19 Histologic Score				
≤ 150	22/26	0.85 (0.65 to 0.96)	[redacted]	[redacted]
> 150	47/56	0.84 (0.72 to 0.92)	[redacted]	[redacted]
DE/HGBCL[c]				
HGBCL: MYC+, BCL2+, BCL6+ (triple hit by FISH)			1/1	1.0

	Primary Analysis		24-Month Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)		Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	101		[redacted]	
Subgroup	**n/N[a]**	**ORR (95% CI)[b]**	**n/N[a]**	**ORR (95% CI)[b]**
HGBCL: MYC+, BCL2+ or BCL6+ (double hit by FISH)			3/3	1.0
HGBCL NOS: MYC– (by FISH), Ki67 > 70% (by IHC)			2/2	1.0
Overall HGBCL			6/6	1.0
Co-expression of MYC and BCL2 (double expressor lymphoma by IHC)			24/27	0.89

BCL = B-cell lymphoma; CI = confidence interval; CSR = Clinical Study Report; DE/HGBCL = double expressor and high-grade B-cell lymphoma; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; HGBCL = high-grade B-cell lymphoma; IHC = immunohistochemistry; NOS = not otherwise specified; NR = not reported; ORR = objective response rate; PMBCL = primary mediastinal large B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

[a] n/N signifies the number (n) who achieved an objective response out of the total number (N) evaluable for a given subgroup. N does not total to 101 for all subgroups because not all characteristics were evaluable for each patient.

[b] 95% CIs of ORR using Clopper–Pearson method.

[c] Sample size for lymphoma subtype was small. This is because it was not tested or evaluable in 61 patients, six patients were not HGBCL, and one patient tested negative.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off)[32] and Neelapu et al. 2017.[35] For 24-month Analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Table 42: Secondary Clinical Effectiveness Outcomes (Investigator Assessment) (Modified Intention-to-Treat)

	Primary Analysis, All Patients			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
DOR[a]						
Number of patients with response (CR or PR) by cut-off date	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	84
DOR (CR or PR) time, KM median (95% CI), months	[redacted]	[redacted]	8.1 (3.3, NE)	[redacted]	[redacted]	[redacted]
Type of Events (Resulting in End of Response)						
Disease progression, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease- or treatment- related death, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censoring Reason						
Response ongoing (CR or PR) at cut-off date, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Started new anticancer therapy, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allogeneic SCT while in response, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients in response (KM estimate) at 6 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients in response (KM estimate) at 12 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients in response (KM estimate) at 24 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS[b]						

	Primary Analysis, All Patients			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Number of patients	77	24	101	77	24	101
Number of patients censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS time, KM median (95% CI), months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of Events (Resulting in End of PFS)						
Disease progression, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease- or treatment- related death, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Censoring Reason						
Response or stable disease ongoing at cut-off date, n	[redacted]	[redacted]	45	[redacted]	[redacted]	[redacted]
Started new anticancer therapy, n	[redacted]	[redacted]	1	[redacted]	[redacted]	[redacted]
Allogeneic SCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients with PFS (KM estimate) at 6 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients with PFS (KM estimate) at 12 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients with PFS (KM estimate) at 24 months, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ongoing Response						
Number of patients who could be evaluated	77	24	101	77	24	101
Number of patients with ongoing responses (CR or PR) at cut-off date, n (%)	[redacted]	[redacted]	44 (44)	[redacted]	[redacted]	39 (39)[c]

	Primary Analysis, All Patients			24-Month Analysis		
	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	Cohort I (DLBCL)	Cohort II (PMBCL, TFL)	Cohort I and Cohort II (DLBCL, PMBCL, TFL)
Number of patients with ongoing CR at cut-off date, n (%)	[redacted]	[redacted]	39 (39)	[redacted]	[redacted]	37 (37)
Number of patients with ongoing PR at cut-off date, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2 (2)

CI = confidence interval; CR = complete response; CSR = Clinical Study Report; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; KM = Kaplan–Meier; NA = not applicable; NE = not estimable; NR = not reported; OS = overall survival; PFS = progression-free survival; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response; SCT = stem cell transplant.

Note: Disease status used is the investigator assessment of disease status per Cheson et al. (2007) for the modified intention-to-treat data set.[69] KM estimates provide the probability of being in response (having DOR) or of PFS, for DOR and PFS, respectively.

[a] DOR was defined only for patients with objective response and was the time from the first objective response to disease progression or to death due to disease relapse or drug-related toxicity. In the primary analysis, DOR was censored for ongoing response or the start of new anticancer therapy (*excluding* SCT). In the 24-month analysis, DOR was censored for ongoing response or the start of new anticancer therapy (*including* SCT received while in response).

[b] PFS was defined as the time from the axicabtagene ciloleucel infusion date to the date of disease progression or death from any cause. In the primary analysis, PFS was censored for ongoing response or the start of new anticancer therapy (excluding SCT). In the 24-month analysis, PFS was censored for ongoing response or the start of new anticancer therapy (including stem cell transplant).

[c] Two of the patients with ongoing responses underwent allogeneic SCT while in axicabtagene ciloleucel–induced response.

Source: For primary analysis — Information submitted by manufacturer (CSR, January 27, 2017, data cut-off)[32] and Neelapu et al. 2017.[35] For 24-month analysis — Information submitted by manufacturer (24-month addendum to CSR, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Table 43: Subgroup Analysis of Progression-Free Survival Rate (Investigator Assessment) (Modified Intention-to-Treat)

	Primary Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	**101**	
Subgroup	**n/N[a]**	**PFS Rate (95% CI)[b]**
Overall	[redacted]	[redacted]
Number of prior chemotherapies		
1	[redacted]	[redacted]
2 to 3	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]
Type of lymphoma		
DLBCL	[redacted]	[redacted]
PMBCL	[redacted]	[redacted]
TFL	[redacted]	[redacted]
Age at baseline		
< 65 years	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]
Sex		
Male	[redacted]	[redacted]

	Primary Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	101	
Subgroup	**n/N[a]**	**PFS Rate (95% CI)[b]**
Female	[redacted]	[redacted]
Race		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
ECOG performance status		
Score of 0	[redacted]	[redacted]
Score of 1	[redacted]	[redacted]
Refractory to first-line therapy		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Refractory to ≥ 2 consecutive lines of therapy		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Relapsed/refractory status		
Primary refractory	[redacted]	[redacted]
Refractory to ≥ second-line therapy	[redacted]	[redacted]
Relapsed to ≥ second-line therapy		
Relapsed post-autologous SCT	[redacted]	[redacted]
Tumour burden at the time of therapy		
≤ median	[redacted]	[redacted]
> median	[redacted]	[redacted]
Stage of disease		
I to II	[redacted]	[redacted]
III to IV	[redacted]	[redacted]
CD19 at baseline (histological score)		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
CD19 histologic score		
≤ 150	[redacted]	[redacted]
> 150	[redacted]	[redacted]

CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; KM = Kaplan–Meier; PFS = progression-free survival; PMBCL = primary mediastinal large B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

Note: PFS rate is estimated per KM method.

[a] n/N signifies the number (n) of patients at risk out of the total number (N) evaluable for a given subgroup. N does not total to 101 for all subgroups because not all characteristics were evaluable for each patient.

[b] 95% CI are the upper and lower 95% confidence limits of PFS rate KM estimates.

Source: Information submitted by manufacturer (Clinical Study Report, January 27, 2017, data cut-off).[32]

Table 44: Subgroup Analysis of Ongoing Response Rate (Investigator Assessment) (Modified Intention-to-Treat)

	24-Month Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	101	
Subgroup	**n/N [a]**	**ORR (95% CI) [b]**
Overall	39/101	0.39 (0.29 to 0.49)
Number of prior chemotherapies		
1	[redacted]	[redacted]
2 to 3	[redacted]	[redacted]
≥ 4	[redacted]	[redacted]
Type of lymphoma		
DLBCL	25/77	0.32 (0.22 to 0.44)
PMBCL	5/8	0.63 (0.24 to 0.91)
TFL	9/16	0.56 (0.30 to 0.80)
Cell of origin		
Germinal center B-cell–like subtype	20/49	0.41 (0.27 to 0.56)
Activated B-cell–like subtype	6/17	0.35 (0.14 to 0.62)
Unclassified	[redacted]	[redacted]
Age at baseline		
< 65 years	29/77	0.38 (0.27 to 0.49)
≥ 65 years	10/24	0.42 (0.22 to 0.63)
Sex		
Male	[redacted]	[redacted]
Female	[redacted]	[redacted]
Race		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Other	[redacted]	[redacted]
ECOG performance status		
Score of 0	18/42	0.43 (0.28 to 0.59)
Score of 1	21/59	0.36 (0.24 to 0.49)
Refractory to first-line therapy		
Yes	10/26	0.38 (0.20 to 0.59)
No	[redacted]	[redacted]
Refractory to ≥ 2 consecutive lines of therapy		
Yes	18/53	0.34 (0.22 to 0.48)
No	[redacted]	[redacted]
Relapsed/refractory status		
Primary refractory	[redacted]	[redacted]
Refractory to ≥ second-line therapy	28/77	0.36 (0.26 to 0.48)
Relapsed to ≥ second-line therapy	[redacted]	[redacted]

	24-Month Analysis	
	Cohort I and Cohort II (DLBCL, PMBCL, TFL)	
Total sample size (number of patients who could be evaluated), N	**101**	
Subgroup	**n/N [a]**	**ORR (95% CI) [b]**
Relapsed post-autologous SCT	11/21	0.52 (0.30 to 0.74)
Tumour burden at the time of therapy		
≤ median	[redacted]	[redacted]
> median	[redacted]	[redacted]
Stage of disease		
I to II	9/15	0.60 (0.32 to 0.84)
III to IV	30/86	0.35 (0.25 to 0.46)
CD19 at baseline (histological score)		
Positive	30/74	0.41 (0.29 to 0.53)
Negative	4/8	0.50 (0.16 to 0.84)
CD19 histologic score		
≤ 150	[redacted]	[redacted]
> 150	[redacted]	[redacted]
BCL2 alterations/overexpression		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
BCL6 alterations/overexpression		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
C-MYC alterations/overexpression		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Double hit		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Triple hit		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]

BCL = B-cell lymphoma; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; PMBCL = primary mediastinal large B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

[a] n/N signifies the number (n) of patients with ongoing response of the total number (N) evaluable for a given subgroup. N does not total to 101 for all subgroups because not all characteristics were evaluable for each patient.

[b] 95% CIs of ORR using Clopper–Pearson method.

Source: Information submitted by manufacturer (24-month addendum to Clinical Study Report, August 11, 2018, data cut-off)[34] and Locke et al. 2019.[37]

Table 45: Subsequent Therapies (Investigator Assessment) (Modified Intention-to-Treat)

	24-Month Analysis	
	Phase I	**Cohort I and Cohort II, (DLBCL, PMBCL, TFL)**
Sample size, N	[redacted]	[redacted]
Subsequent Anticancer Therapy		
Incidence of subsequent chemotherapy, n (%)	[redacted]	[redacted]
Incidence of autologous SCT (received while in remission after axicabtagene ciloleucel), n (%)	[redacted]	0 (0)
Incidence of allogeneic SCT (received while in remission after axicabtagene ciloleucel), n (%)	[redacted]	2 (2)
Incidence of autologous SCT (received while relapsing post-axicabtagene ciloleucel), n (%)	[redacted]	[redacted]
Incidence of allogeneic SCT (received while relapsing post-axicabtagene ciloleucel), n (%)	[redacted]	[redacted]

DLBCL = diffuse large B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

Note: The investigator's assessment of disease per Cheson et al. (2007) was used.[69]

Source: Information submitted by manufacturer (manufacturer response, Feb 1, 2019; data cut-off not reported),[79] and Locke et al. 2019.[37]

Appendix 9: Relevant Studies Published in Conference Abstracts

There were 11 conference abstracts that contained data from 11 studies distinct from the ZUMA-1 pivotal trial. The eligibility of these abstracts could not be established definitively for this systematic review (see Table 1), as we were not able to ascertain the number of lines of previous therapy, and therefore we do not know whether the study patients met the Health Canada–approved indication for axicabtagene ciloleucel. All of the conference abstracts were published in 2018 or 2019 and were conducted in the US. Study designs were described as retrospective cohort (three studies),[89,91,92] multi-centre retrospective cohort (three studies),[73,74,90] non-randomized (one study),[76] phase II safety management study (one study),[95] observational study (biorepository-clinical outcome protocol; one study),[75] or observational (not otherwise specified; two studies).[88,93]

Across the included conference abstracts, the sample size ranged from eight[76] to 165.[74] Patient characteristics were reported incompletely in the abstracts but five studies included at least some patients who would not have been eligible for inclusion in ZUMA-1,[73-76,93] two studies included patients with Eastern Cooperative Oncology Group status greater than one,[73,74] and at least three studies explicitly reported allowance for bridging therapy.[73-75] Reported efficacy and safety outcomes were similar to those in ZUMA-1, with the exception of two abstracts that included measures of patient-reported symptoms or quality of life.[93,95]

In terms of the primary efficacy outcome of interest reported in ZUMA-1, a measure of objective response rate (ORR) was reported in four abstracts, although the precise definition of ORR was unclear in these reports.[73-75,88] In three abstracts, which included 211, 25, and 22 patients, ORR was reported at approximately day 28 to day 30, and ranged from 79%[74] to 86%.[75,88] In the fourth abstract, the best ORR at four months among those treated with axicabtagene ciloleucel was reported as 64.4% (or 57% in the intention-to-treat analysis set).[73]

With respect to notable harms, cytokine release syndrome (CRS) was reported in seven abstracts.[73-75,89-92] The prevalence of any grade of CRS ranged from 83% (among a subset of patients aged 65 years or older)[91] to 100%.[92] CRS greater than or equal to grade 3 was reported in five abstracts,[73-75,89,91] and ranged from 0%to 17%.[75,73] The prevalence of grade 5 CRS was documented in two abstracts at 0% or 2.6%,[75,73] and was not reported in four abstracts.[74,89,90,92]

Neurological events or neurotoxicity were reported in three abstracts.[73] In one abstract, 76.3% of patients had any grade of neurotoxicity, 38.2% had grade 3 or higher, and 1.3% had grade 5.[73] In a second abstract, 31% of patients had neurological events with grade 3 or higher and 0% with grade 5,[74] and in the final abstract, 64% of patients had any grade of neurotoxicity with 27% having grade 3 or grade 4.[75] One abstract reported the overall prevalence of chimeric antigen receptor-related encephalopathy syndrome as 58% or 71% for patients aged 65 and older and for those younger than 65 years, respectively.[91]

Persistent cytopenia was reported as occurring in 46% of patients in one abstract.[90] Information on infections was reported incompletely.

Two abstracts included measures of patient-reported symptoms of adverse events (as measured with the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events) or health-related quality of life (i.e., EuroQol 5-Dimensions

questionnaire [EQ-5D] and the Short Form [36] Health Survey).[93,95] In one abstract (n = 29), the most common patient-reported symptoms at 14 days — the peak time of reported symptoms — following axicabtagene ciloleucel infusion were decreased appetite (95% any severity, 48% moderate to severe), fatigue (95% any severity, 43% moderate to severe) and dry mouth (85% any severity, 38% moderate to severe).[93]

At 90 days post-treatment, there were no moderate to severe symptoms reported; the most common symptoms of any severity were fatigue (82%), insomnia (55%) and joint pain (45%).[93] The change in physical quality of life or mental health quality of life from baseline to 90 days following treatment with axicabtagene ciloleucel was not statistically significant.[93] In the second abstract (n = 34), EQ-5D-3 levels (3L) health utility values were estimated from the EQ-5D-5 levels (5L) instrument by using a mapping algorithm and by applying the US valuation set to produce index scores. Mean values were reported as 0.80 (standard deviation 0.17) at screening, 0.74 (standard deviation 0.15) at week 4, 0.80 (standard deviation 0.13) at month 3 and 0.82 (standard deviation 0.21) at month 6 (no statistical comparisons).[95] A health utility decrement (disutility) of 0.05 was reported to be associated with the timing of the axicabtagene ciloleucel–related toxicities at week 4, but no statistical comparison with baseline was reported.[95] As well, at the six-month assessment, utilities were available for only seven of the 34 patients, making any change over time difficult to interpret.

There was insufficient information from the non-pivotal studies in the published conference abstracts to permit a detailed critical appraisal of the studies reported therein. Some high-level limitations across the non-pivotal studies, identified from the abstracts, include the following: lack of comparators or control group, undefined outcome criteria including definitions and timing of assessments, and limited patient characteristics provided, thus affecting the assessment of generalizability. The evidence presented on the non-pivotal studies from the conference abstracts should be interpreted in light of the limited information available.

Table 46: Characteristics of Studies Published in Conference Abstracts

Study Citation, Country, Funding Source, COI Declarations	Study Objective(s), Design and Setting, Analytical Approach, Duration	Patient Characteristics — Inclusion and Exclusion Criteria, Sampling Procedure, Subgroups	Intervention(s) and Comparator(s)	Outcomes
Jacobson et al. (2018)[73] US **Funding source:** NR **COI declarations:** Authors declared receipt of fees (e.g., advisory board, consulting, research funding, honorariums or other) from, or equity interest in, various companies, including Kite, Novartis, and Gilead.	**Study objective(s):** To study efficacy and safety of axicabtagene ciloleucel in a real-world setting where eligibility/management considerations may diverge from clinical trials. **Study design:** Multi-centre retrospective cohort study **Study setting:** NR **Analytical approach:** 95% exact binomial CIs; analysis done in complete sample (referred to as ITT set) and in treated patients (treated set). Univariate analyses within subgroups for efficacy (response), CRS, and neurotoxicity **Follow-up duration:** Median follow-up 4.0 months	**Inclusion criteria:** NR **Exclusion criteria:** NR **Recruitment/sampling procedure:** NR **Subgroups:** • ECOG performance status (0, 1, 2, 4) • Tumour bulk (< 5, 5 to 10, > 10) • IPI risk category (0 to 1, 2, 3, 4 to 5) • Double hit (yes, no) • Triple hit (yes, no) • Grade 3+ CRS (yes, no) • Grade 3+ neurotoxicity (yes, no) • Bridging therapy (yes, no) • Prior ibrutinib (yes, no) • Prior lenalidomide (yes no) • Tocilizumab use (yes, no) • Steroid use (high dosage, < 5 dosages, ≤ 5 dosages, none)	**Intervention:** Axicabtagene ciloleucel; dose and dosage schedule NR Bridging chemotherapy followed pheresis in 36% of patients Conditioning chemotherapy NR **Comparator:** None	Best ORR, CRR, CR, PR, PD, OS, CRS, NT, CAR T-cell levels Primary end point was not specified
Jim et al. (2018)[93] US **Funding source:** NR **COI declarations:** Authors declared consultancy or scientific advice for pharmaceutical	**Study objective(s):** To evaluate patient-reported outcomes and neurocognitive functioning in adult patients in the first 90 day after treatment with axicabtagene ciloleucel **Study design:** Reported as an observational study **Study setting:** Moffitt Cancer Center	**Inclusion criteria:** NR **Exclusion criteria:** NR **Recruitment/sampling procedure:** Patients who were scheduled to undergo axicabtagene ciloleucel therapy as part of a clinical trial or standard of care at Moffitt Cancer Center were recruited prior to conditioning chemotherapy; “52% treated on an interventional trial”	**Intervention:** Axicabtagene ciloleucel; dose and dosage schedule NR Conditioning chemotherapy NR **Comparator:** None	Symptoms likely to be of concern to cancer patients (e.g., fatigue, insomnia, diarrhea, constipation, nausea, decreased appetite; assessed with PRO-CTCAE); QoL (SF-36); neurocognitive function (RBANS) Primary end point is not specified

Study Citation, Country, Funding Source, COI Declarations	Study Objective(s), Design and Setting, Analytical Approach, Duration	Patient Characteristics — Inclusion and Exclusion Criteria, Sampling Procedure, Subgroups	Intervention(s) and Comparator(s)	Outcomes
companies, including Kite Pharma.	**Analytical approach:** Means, standard deviations, frequencies, and Wilcoxon signed rank tests were used to characterize outcomes and change over time **Follow-up duration:** 90 days	**Subgroups:** NR		
Nastoupil et al. (2018)[74] US **Funding source:** NR **COI declarations:** Authors declared receipt of fees (e.g., consulting, research funding, honorariums or other) from, or equity interest in, various companies, including Kite, Novartis, and Gilead	**Study objective(s):** Evaluated real-world outcomes (efficacy and safety) of patients treated with standard of care axicabtagene ciloleucel under the commercial FDA label **Study design:** Multi-centre retrospective study **Study setting:** 17 US academic centres **Analytical approach:** Frequencies were used to characterize outcomes. **Follow-up duration:** 30 days, and 100 days	**Inclusion criteria:** NR (Reported that 49% would not have met eligibility criteria for ZUMA-1 at time of leukapheresis) **Exclusion criteria:** NR **Recruitment/sampling procedure:** NR **Subgroups:** NR	**Intervention:** Axicabtagene ciloleucel; dose and dosage schedule NR Bridging therapy followed apheresis in 56% of patients Conditioning chemotherapy NR **Comparator:** None	ORR, CR, PR, SD, PD, CRS, NE, tocilizumab use, corticosteroid use, death, hospitalization Primary end point is not specified
Spiegel et al. (2018)[75] US **Funding source:** NR **COI declarations:** Authors declared receipt of fees (e.g., speaker, consulting,	**Study objective(s):** Describe CAR T expansion and its correlation with clinical outcomes in patients treated with commercial axicabtagene ciloleucel **Study design:** Observational study (biorepository-clinical outcome protocol) **Study setting:**	**Inclusion criteria:** NR (36% of infused patients would not have met eligibility criteria for ZUMA-1) **Exclusion criteria:** NR **Recruitment/sampling procedure:** Studied 25 patients with aggressive lymphoma who were consecutively apheresed	**Intervention:** Commercial axicabtagene ciloleucel; dose and dosage schedule NR 9 patients received bridging therapy prior to lymphodepletion chemotherapy (36%) (chemo = 4, radiation = 2,	ORR, CR, PR, CRS, neurotoxicity, expansion of CAR T cells Primary end point is not specified

Study Citation, Country, Funding Source, COI Declarations	Study Objective(s), Design and Setting, Analytical Approach, Duration	Patient Characteristics — Inclusion and Exclusion Criteria, Sampling Procedure, Subgroups	Intervention(s) and Comparator(s)	Outcomes
research funding, or other) from, or equity interest in, various companies, including Kite, Novartis, and Gilead	Stanford University Medical Center **Analytical approach:** Median, frequencies, and correlations were used to characterize outcomes **Follow-up duration:** Followed for a minimum of 7 days or until adverse events resolved to < grade 2. Median hospitalization was 13.5 days (range 7 to 44)	**Subgroups:** NR	high-dose dexamethasone = 3) Conditioning chemotherapy NR **Comparator:** None	
Sano et al. (2018)[91] US **Funding source:** NR **COI declarations:** Authors declared receipt of fees (e.g., honorariums, research funding, membership on board of directors, advisory committees or other) from, or equity interest in, various companies, including Kite, Novartis, and Gilead	**Study objective(s):** Report safety outcomes in elderly patients (> 65 years) with large B-cell lymphoma treated with axicabtagene ciloleucel at their institution **Study design:** Retrospective cohort study **Study setting:** University of Texas, MD Anderson Cancer Center **Analytical approach:** Frequencies were used to characterize outcomes and change over time. **Follow-up duration:** At least 30 days	**Inclusion criteria:** Relapsed or refractory DLBCL, PMBCL, HGBCL, and TFL **Exclusion criteria:** NR **Recruitment/sampling procedure:** NR **Subgroups:** • < 65 years of age • ≥ 65 years of age	**Intervention:** Conditioning chemotherapy with cyclophosphamide and fludarabine for 3 days followed by axicabtagene ciloleucel infusion after 2 days of rest at a dose of 2 x 10^6 CAR T cells/kg body weight **Comparator:** NR	CR, PR, SD, PD, CRS, death, CRES (i.e., neurological toxicity), hospitalization period Primary end point is not specified
Oak et al. (2018)[88] US **Funding source:** NR	**Study objective(s):** To characterize the observed mechanisms of treatment failure following axicabtagene ciloleucel therapy	**Inclusion criteria:** Refractory large B-cell lymphoma; WHO diagnosis and B-cell antigen expression **Exclusion criteria:** NR	**Intervention:** Axicabtagene ciloleucel following referral; dose and dosage schedule NR	ORR, CR, PR, SD, PD, CAR T-cell levels

Study Citation, Country, Funding Source, COI Declarations	Study Objective(s), Design and Setting, Analytical Approach, Duration	Patient Characteristics — Inclusion and Exclusion Criteria, Sampling Procedure, Subgroups	Intervention(s) and Comparator(s)	Outcomes
COI declarations: No relevant conflicts of interest to declare	**Study design:** Observational study **Study setting:** Stanford University Medical Center **Analytical approach:** Frequencies were used to characterize outcomes **Follow-up duration:** Peripheral blood CAR T-cell numbers at days 7, 14, 21, and 28 - Disease response at day 28, and 3 months	**Recruitment/sampling procedure:** NR **Subgroups:** NR	Conditioning chemotherapy NR **Comparator:** none	Primary end point is not specified
Lin et al. (2018)[52] US **Funding source:** Kite/Gilead **COI declarations:** Authors declared to be employees and equity owners of Kite, a Gilead company.	**Study objective(s):** To report the EQ-5D-5L ad hoc analysis results from a phase II safety management study of axicabtagene ciloleucel **Study design:** Phase II, safety management study **Study setting:** NR **Analytical approach:** EQ-5D-5L scores were mapped onto EQ-5D-3L scores, which were converted to EQ-5D-3L index scores using the US valuation algorithm. Descriptive analysis of outcomes (means, medians, standard deviations, standard errors, and frequencies)	**Inclusion criteria:** NR; **Exclusion criteria:** NR **Recruitment/sampling procedure:** NR; patients in the safety measurement study **Subgroups:** Health states (progression-free, progressed disease, death)	**Intervention:** Axicabtagene ciloleucel therapy Conditioning chemotherapy NR **Comparator:** None	EQ-5D-3L index scores, disutility (healthy utility decrement) Primary end point is not specified

Study Citation, Country, Funding Source, COI Declarations	Study Objective(s), Design and Setting, Analytical Approach, Duration	Patient Characteristics — Inclusion and Exclusion Criteria, Sampling Procedure, Subgroups	Intervention(s) and Comparator(s)	Outcomes
	Follow-up duration: Median follow-up duration (min, max) was 5.1 (0.3, 9.5) months			
Faramand et al. (2019)[89] US **Funding source:** NR **COI declarations:** NR	**Study objective(s):** To report the results of cytokine analysis using a point-of-care device to predict immune-related toxicities in patients with relapsed/refractory DLBCL treated with axicabtagene ciloleucel **Study design:** Retrospective cohort study **Study setting:** NR **Analytical approach:** Frequencies **Follow-up duration:** NR	**Inclusion criteria:** Patients with relapsed/refractory DLBCL **Exclusion criteria:** NR **Recruitment/sampling procedure:** NR **Subgroups:** NR	**Intervention:** Commercial axicabtagene ciloleucel therapy Conditioning chemotherapy NR **Comparator:** None	Serum cytokine levels of IL-6, L-15, ANG2/ANG1 ratio, CRS Primary end point is not specified
Nahas et al. (2019)[90] US **Funding source:** NR **COI declarations:** NR	**Study objective(s):** To report persistent cytopenias after T-cell therapy following axicabtagene ciloleucel infusion **Study design:** Retrospective study **Study setting:** Sylvester **Comprehensive** Cancer Center, University of Miami **Health System** **Analytical approach:** Frequencies were used to characterize outcomes	**Inclusion criteria:** Patients with CD19+ relapsed or refractory B-NHL who received commercial axicabtagene ciloleucel at the Sylvester **Comprehensive** Cancer Center, University of Miami **Health System** **Exclusion criteria:** NR **Recruitment/sampling procedure:** All patients treated with commercial axicabtagene ciloleucel through 10/12/18 **Subgroups:** NR	**Intervention:** Axicabtagene ciloleucel therapy Conditioning chemotherapy NR **Comparator:** None	Platelet count, CRS, persistent cytopenias after T-cell therapy (patients who were alive 30 days after axicabtagene ciloleucel infusion and did not have ANC > 500 cells/mL without growth factor support), ANC Primary end point is not specified

Study Citation, Country, Funding Source, COI Declarations	Study Objective(s), Design and Setting, Analytical Approach, Duration	Patient Characteristics — Inclusion and Exclusion Criteria, Sampling Procedure, Subgroups	Intervention(s) and Comparator(s)	Outcomes
	Follow-up duration: At least 30 days			
Byrne et al. (2019)[76] US **Funding source:** NR **COI declarations:** NR	**Study objective(s):** To compare the experience of receiving axicabtagene ciloleucel in a real-world setting with the experience of receiving axicabtagene ciloleucel on ZUMA-1 clinical trial **Study design:** Non-randomized study **Study setting:** NR **Analytical approach:** Frequencies and mean were used to characterize outcomes **Follow-up duration:** Median 78.5 days, for patients receiving commercial axicabtagene ciloleucel	**Inclusion criteria:** NR; reported as being similar to ZUMA-1 **Exclusion criteria:** NR; reported as being similar to ZUMA-1 **Recruitment/sampling procedure:** NR; ZUMA-1 patients enrolled January 2016 to February 2017 Non-ZUMA-1 patients enrolled November 2017 to August 2018 **Subgroups:** NR	**Intervention:** Commercial axicabtagene ciloleucel therapy (non-ZUMA-1) Conditioning chemotherapy NR **Comparator:** ZUMA-1 patients on axicabtagene ciloleucel therapy; no treatment	Response, PR, CR, SD, disease progression, survival
Maakaron et al. (2019)[92] US **Funding source:** NR **COI declarations:** Authors declared consultancy, research funding, membership on board of directors or advisory committees with	**Study objective(s):** To evaluate the utility of PCT as an infectious biomarker in patients undergoing commercial treatment with axicabtagene ciloleucel **Study design:** Retrospective study **Study setting:** 2 institutions **Analytical approach:** Frequencies, median were used to characterize outcomes	**Inclusion criteria:** Patients who received axicabtagene ciloleucel for relapsed or refractory aggressive B-cell lymphoma and had PCT levels checked during their admission **Exclusion criteria:** NR **Recruitment/sampling procedure:** NR **Subgroups:** NR	**Intervention:** Commercial axicabtagene ciloleucel therapy Conditioning chemotherapy NR **Comparator:** None	CRS, body temperature, neutrophil count (median and absolute), antibiotic use (levofloxacin prophylaxis, intravenous antibiotics), infections, PCT, death, PD, vasopressor use

Study Citation, Country, Funding Source, COI Declarations	Study Objective(s), Design and Setting, Analytical Approach, Duration	Patient Characteristics — Inclusion and Exclusion Criteria, Sampling Procedure, Subgroups	Intervention(s) and Comparator(s)	Outcomes
various companies, including Kite, Novartis, and Gilead	**Follow-up duration:** NR			

ANC = absolute neutrophil count; CAR = chimeric antigen receptor; CI = confidence interval; COI = conflict of interest; CR = complete response or complete remission; CRES = CAR-related encephalopathy syndrome; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HGBCL = high-grade B-cell lymphoma; IPI = International Prognostic Index; ITT = intention-to-treat; NR = not reported; NE = neurologic events; ORR = objective response rate; OS = overall survival; PCT = procalcitonin; PD = progressive disease; PMBCL = primary mediastinal large B-cell lymphoma; PR = partial response or partial remission; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; QoL = quality of life; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SD = stable disease; SF-36 = Short Form (36) Health Survey; TFL = transformed follicular lymphoma; WHO = World Health Organization.

Note: Not all abbreviations were defined within the abstracts.

Table 47: Baseline Patient Characteristics of Studies Published in Conference Abstracts

Study Citation	Sample Size and Patient Disposition	Demographic Information	Disease Type, Stage (at Study Entry), CD19 Status, ECOG Performance Status, Relapse/Refractory Status	Prior Therapy (e.g., Number of Previous Chemotherapy Regimens, Prior Autologous/Allogeneic Transplant)
Jacobson et al. (2018)[73]	N = 76 n = 73 evaluable (ITT set) n = 65 treated (treated set) n = 11 pheresed but not treated	**Age:** Median 64.4 years **Sex:** NR **Race:** NR	**Disease type, n (%):** DLBCL, 36 (47.4) HGBL, 10 (13.2) PMBCL, 5 (6.6) Transformed FL, 17 (22.4) Transformed MZL, 4 (5.3) Transformed CLL, 1 (1.3) T-cell histocyte rich, 2 (2.6) HGFL, 1 (1.3) **ECOG PS, n (%):** 0: 19 (25.0) 1: 51 (67.1) 2: 5 (6.6) 3: 0 (0) 4: 1 (1.3) **IPI pre-lymphodepletion, n (%):** 0: 2 (2.6) 1: 12 (15.8) 2: 25 (32.9) 3: 19 (25.0) 4: 15 (19.7) 5: 3 (3.9)	**Prior autologous transplant, n (%):** 23 (30.3) **Prior allogeneic transplant, n (%):** 1 (1.3) **Bridging therapy, n (%):** 27 (35.5) **Prior lenalidomide, n (%):** 18 (23.7) **Prior ibrutinib, n (%):** 8 (10.5) **Number of prior lines of therapy, n (%):** 1: 2 (3) 2: 31 (43) 3: 15 (20) 4+: 26 (34)
Jim et al. (2018)[93]	N = 29	**Age:** Mean ± standard deviation: 58 ± 13 years **Sex:** 28% female **Race:** NR	**Disease type, %:** DLBCL, 76 FL or TFL, 10 MLBCL, 3 Other, 11 Other characteristics NR	NR

Study Citation	Sample Size and Patient Disposition	Demographic Information	Disease Type, Stage (at Study Entry), CD19 Status, ECOG Performance Status, Relapse/Refractory Status	Prior Therapy (e.g., Number of Previous Chemotherapy Regimens, Prior Autologous/Allogeneic Transplant)
Nastoupil et al. (2018)[74]	N = 211 (leukapheresed) n = 165 infused n = 23 scheduled for axicabtagene ciloleucel infusion n = 23 pheresed but not treated n = 163 evaluable for safety n = 112 evaluable for response at day 30	Data from 134/165 pts infused **Age:** Median age (range): 59 (21 to 82) **Sex:** 57% male **Race:** NR	**Disease type, %:** DLBCL including HGBCL, 61 TFL, 31 PMBCL, 8 **ECOG PS, %:** 0 to 1: 81 2: 16 3: 3 Other characteristics NR	**Prior autologous stem cell transplant, %:** 31 **Bridging therapy, %:** 56 **Checkpoint inhibitor therapy, n:** 7 **Prior CD19 CAR T-cell therapy, n**:4 **Prior allogeneic transplant, n**: 2
Spiegel et al. (2018)[75]	N = 25 n = 22 infused n = 3 pheresed but not treated	**Age:** NR **Sex:** NR **Race:** NR	**Disease type, %:** DLBCL (“aggressive lymphoma”) Other characteristics NR	**Bridging therapy, n**: 9 (36%) (chemo = 4, radiation = 2, high dose dexamethasone = 3)
Sano et al. (2018)[91]	N = 61 ≥ 65 years old, n = 17 < 65 years old, n = 44	**Age:** Median age (range), years: ≥ 65: 68 (64 to 77); < 65: 48 (24 to 64); **Sex, n (%):** ≥ 65: Male: 11 (65); Female: 6 (35); < 65: Male: 27 (61); Female: 17 (39); **Race:** NR	**Disease type, n (%):** ≥ 65: DLBCL, including HGBCL: 13(76) TFL: 4(24) PMBCL: 0(0) < 65: DLBCL, including HGBCL: 29(66) TFL: 4(9) PMBCL: 11(25)	NR
Oak et al. (2018)[88]	N = 22 (infused) n = 69 referred for therapy	**Age:** NR **Sex:** NR	**Disease type, n (%):** DLBCL: 11 (50) TFL: 5 (23)	NR

Study Citation	Sample Size and Patient Disposition	Demographic Information	Disease Type, Stage (at Study Entry), CD19 Status, ECOG Performance Status, Relapse/Refractory Status	Prior Therapy (e.g., Number of Previous Chemotherapy Regimens, Prior Autologous/Allogeneic Transplant)
		Race: NR	HGBCL: 2 (1) PMBCL: 2 (1) HGBCL with rearrangement of MYC and BCL2 or BCL6: 2 (1)	
Lin et al. (2018)[52]	N = 34 (treated)	**Age:** Median age (range), years: 51 (21 to 74) **Sex:** 56% male **Race:** NR	**Disease type:** 100% relapsed or refractory large B-cell lymphoma **ECOG PS, %:** 1:56% **IPI, %:** ≥ 3: 32%	NR
Faramand et al. (2019)[89]	N = 20 (treated)	**Age:** Median age (range), years: 64 (43 to 73) **Sex:** NR **Race:** NR	**Disease type, %:** 100% relapsed/refractory DLBCL	NR
Nahas et al. (2019)[90]	N =15 (infused) n = 13 (evaluable) Reasons for not being evaluable: n = 1 died from cerebral edema on day 7 n = 1 not yet reached for 30-day follow-up	**Age:** NR **Sex:** NR **Race:** NR	**Disease type, %:** 100% CD19+ relapsed or refractory B-NHL	NR
Byrne et al. (2019)[76]	Commercial axicabtagene ciloleucel (non-ZUMA-1): N = 25 (enrolled) n = 8 (treated) n = 10 (became ineligible)	**Age:** Mean age, years: Non-ZUMA-1: 56.0 ZUMA-1: 64.8 (NS)	**Volume of disease lesion size, cm^2:** Non-ZUMA-1: 16.4 ZUMA-1: 36 (NS)	**Priori lines of chemotherapy, lines:** Non-ZUMA-1: 3.3 ZUMA-1: 4.4 (NS)

Study Citation	Sample Size and Patient Disposition	Demographic Information	Disease Type, Stage (at Study Entry), CD19 Status, ECOG Performance Status, Relapse/Refractory Status	Prior Therapy (e.g., Number of Previous Chemotherapy Regimens, Prior Autologous/Allogeneic Transplant)
	n = 7 (awaiting reimbursement approval) ZUMA-1 controls: N = 5	**Sex:** NR **Race:** NR		**Bridging chemotherapy, n (%):** Non-ZUMA-1: 6 (75)
Maakaron et al. (2019)[92]	N = 30 (treated)	**Age:** Median age (range), years: 61.5 (31 to 77) **Sex:** NR **Race:** NR	**Disease type, %:** 100% relapsed or refractory aggressive B-cell lymphoma	NR

BCL = B-cell lymphoma; CAR = chimeric antigen receptor; DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FL = follicular lymphoma; HGBCL = high-grade B-cell lymphoma; IPI = International Prognostic Index; ITT = intention-to-treat; MLBCL = mediastinal large B-cell lymphoma; NR = not reported; NHL = non-Hodgkin lymphoma; NS = not significant; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma.

Note: Not all abbreviations were defined within the abstracts.

Table 48: Results Reported in Studies Published in Conference Abstracts

Study Citation	Quantitative Findings or Narrative Summary	Authors' Conclusions
Jacobson et al. (2018)[73]	**Treated analysis set** **Best ORR, n (%):** 47 (64.4) **CR, n (%):** 30 (41.1) **PR, n (%):** 17 (23.3) **SD, n (%):** 1 (1.4) **OS at 4 mo, % (95% CI):** 83.5 (74.8 to 93.2) **ITT analysis set** **Best ORR, %:** 57 **CR, %:** 36 **CRS, n (%)** Any grade: 73 (96.1) Grade 3+: 13 (17.1) Grade 3: 8 (10.5) Grade 4: 4 (5.3)	"Retrospective analysis of a multicenter cohort treated in the real world with axicabtagene ciloleucel reveals important distinctions from ZUMA-1. The ORR and CR rate are lower […] This may reflect inclusion of sicker patients with a poorer PS, and/or with different histologies (ie transformation from non-FL). Outcomes were significantly worse in high risk lymphomas, reflected by IPI, PS, tumor bulk, and baseline CRP. Rates of CRS and NT were similar to ZUMA-1, but toxicity was not associated with tumor bulk or response. It was associated with higher peak inflammatory markers and ALC, which may reflect peak CAR T cell levels, as shown previously."

Study Citation	Quantitative Findings or Narrative Summary	Authors' Conclusions
	Grade 5 (death): 2 (2.6) **NT, n (%):** Any grade: 58 (76.3) Grade 3+: 29 (38.2) Grade 3: 24 (31.6) Grade 4: 4 (5.3) Grade 5 (death): 1 (1.3) **Grade 5 events, n (%):** 11 (14.5) PD: 6 (7.9) CRS/NT: 3 (3.9) Infection: 1 (1.3) Cardiomyopathy: 1 (1.3) **Deaths, n:** 11 (6 from PD, 5 from toxicity) **Length of admission, median (range):** 17 (7 to 77) **Readmission, n (%):** 17 (22.4) **ICU care, n (%):** 23 (30.3) **Medications, n (%):** Tocilizumab, any use: 51 (67.1) Tocilizumab, 2+ doses: 33 (43.4) Steroids, low dose, total: 51 (67.1) Steroids, high dose, total: 8 (10.5) Siltuximab: 1 (1.3)	
Jim et al. (2018)[93]	**Most common symptoms at 14 days (peak time of patient-reported symptoms) following axicabtagene ciloleucel** Decreased appetite: 95% any severity, 48% moderate to severe Fatigue: 95% any severity, 43% moderate to severe Dry mouth: 85% any severity, 38% moderate to severe **Most common symptoms at 90 days following axicabtagene ciloleucel** Fatigue: 82% any severity Insomnia: 55% any severity Joint pain: 45% any severity No moderate to severe symptoms at 90 days	"Results indicate that moderate-to-severe patient-reported symptoms were transient following axicabtagene ciloleucel, although a majority of patients reported ongoing, low-grade symptoms at 90 days post-treatment. Quality of life and neurocognition did not significantly change over time. These preliminary findings warrant larger future studies with longer follow-up to better understand changes in PROs and neurocognition in cancer survivors treated with CAR-T."

Study Citation	Quantitative Findings or Narrative Summary	Authors' Conclusions
	Change from baseline to 30 days following axicabtagene ciloleucel Total RBANS percentile score: –8.18, *P* = 0.32 **Change from baseline to 90 days following axicabtagene ciloleucel** Physical health QoL: 1.43, *P* = 0.37 Mental health QoL: 2.66, *P* = 0.07	
Nastoupil et al. (2018)[74]	Time from leukapheresis to start of conditioning chemotherapy (median): 21 days Time from leukapheresis to axicabtagene ciloleucel infusion (median): 26 days Hospitalization period (median): 14 days **Response at day 30 (n = 112 evaluable)** ORR, %: 79 CR, %: 50 PR, %: 29 SD, %: 6 PD, %: 14 **Response at day 100 (n = 39 evaluable)** Ongoing response, %: 59 Ongoing CR, %: 49 Ongoing PR, %: 10 **CRS grade ≥ 3, %:** 7 **NEs %:** Grade ≥3: 31 Grade 5: 0 **Medications, %:** Tocilizumab, 62 Corticosteroids, 57 **Death from AEs post-infusion, n:** 3 (1 from HLH, 1 from systemic candidiasis, 1 from septic shock) **Death due to progressive disease:** NR **Death before infusion, n:** 15	"This multicenter retrospective study delineates the real world outcomes of axicabtagene ciloleucel CAR T-cell therapy for r/r aggressive B-cell lymphoma when used as a standard of care. Though limited by relatively short follow up, 30 day responses in the real world setting are comparable to the best responses observed on the pivotal ZUMA-1 clinical trial. Importantly, safety appears comparable to the ZUMA-1 trial despite nearly half the pts failing to meet ZUMA-1 eligibility criteria."

Study Citation	Quantitative Findings or Narrative Summary	Authors' Conclusions
Spiegel et al. (2018)[75]	Time from initial clinic visit to infusion, days, median (range): 47 (34 to 117) Time from apheresis to infusion, days, median (range): 22 (19 to 38) **Hospitalization**, days, median (range): 13.5 (7 to 44) **At day 28, (n = 22)** ORR, %: 86 CR, %: 45 **At 3 months (n = 15)** ORR, %: 53 CR, n: 7 PR, n:1 Progressed, %: 47 **Median day-7 peak in vivo axicabtagene ciloleucel expansion, CAR-T cells/µL:** 38 **CRS, %** Any grade: 95 Grade 2: 73 ≥ grade 3: 0 **Neurotoxicity** Any grade: 64% Grade 3 or grade 4: 27% **Medications** Tocilizumab, median number of doses: 1 (range 0 to 4) Corticosteroids: 82% Both tocilizumab and steroids: 77% Duration of steroids, days, median (range): 8.5 (range 1 to 30)	"Our analysis of 22 infused axicabtagene ciloleucel patients showed an ORR of 86% and CR of 45%, despite 36% Zuma-1 ineligibilities and steroid use in 82%. Blood CAR-T expansion was associated with both CRS and neurotoxicity but not clinical response. Detection of high concentration of CAR-T cells in affected lymph nodes 2 days post infusion suggests quantification of CAR-T cells at disease sites could be predictive of clinical responses."
Sano et al. (2018)[91]	**CR, n (%):** • ≥ 65 years: 8 (47) • < 65 years: 21 (48) **PR, n (%):**	"Our results suggest that response rates are comparable between the elderly and younger age groups at day 30 after axicabtagene ciloleucel therapy. Importantly, toxicities due to CRS and/or CRES after axicel CD19 CAR T cell therapy are comparable between the elderly (≥65 years) and younger (<65 years) patients with relapsed or refractory large B-cell lymphoma."

Study Citation	Quantitative Findings or Narrative Summary	Authors' Conclusions
	• ≥ 65 years: 5 (29) • < 65 years: 12 (27) **SD, n (%):** • ≥ 65 years: 1 (6) • < 65 years: 3 (7) **PD, n (%):** • ≥ 65 years: 3 (18) • < 65 years: 8 (18) **CRS, overall, %:** • ≥ 65 years: 83 • < 65 years: 91 **CRS, grade 0, n (%):** • ≥ 65 years: 3 (18) • < 65 years: 4 (9) **CRS, grade 1 to 2, n (%):** • ≥ 65 years: 11 (65) • < 65 years: 35 (80) **CRS,** ≥ grade 3, n (%): • ≥ 65 years: 3 (18) • < 65 years: 5 (11) **CRES, overall, %:** • ≥ 65 years: 58 • < 65 years: 71 **CRES, grade 0, n (%):** • ≥ 65 years: 7 (41) • < 65 years: 13 (30) **CRES, grade 1 to 2, n (%):** • ≥ 65 years: 5 (29)	

Study Citation	Quantitative Findings or Narrative Summary	Authors' Conclusions
	• < 65 years: 14 (32) **CRES, ≥ grade 3, n (%):** • ≥ 65: 5 (29) • < 65: 17 (39) **Hospitalization, days, median:** • ≥ 65: 19 • < 65: 15	
Oak et al. (2018)[88]	**Day 28** ORR, %: 86 CR, n: 10 PR, n: 9 SD, n: 1 PD, n: 2 **Day 90 response for those with CR or PR at day 28 (n = 12 evaluable)** Developed PD, n: 5 **No initial response or relapsed after day 28, n/N (%):** 8/22 (36)	"Eight of 22 (36%) of patients who underwent CAR19 infusion did not respond or relapsed after Day 28 response. Five patients (62%) who failed therapy had loss or downregulation of CD19, which emphasizes that single target antigen loss is a common mechanism of CAR-T failure. However, lack of CAR-T cell expansion was noted in multiple patients, suggesting that there may be T cell intrinsic causes of treatment failure. Further studies are necessary to help identify and predict which patients will benefit from targeted immunotherapy."
Lin et al. (2018)[52]	**EQ-5D collected, n** Time of screening: 33 Week 4: 27 Month 3: 20 Month 6: 7 **EQ-5D-5L index scores, mean (SD)** Time of screening: 0.80 (0.17) Week 4: 0.74 (0.15) Month 3 0.80 (0.13) Month 6: 0.82 (0.21) **EQ-5D by health state (regardless of time point)** Progression-free health state: 0.80 (0.14) Progressed disease: 0.72 (0.17) Death: NR	"To our knowledge, this is the first set of health utility values published for R/R-LBCL patients. In this ad hoc analysis, health utility values appear to transiently decrease slightly at one month post CAR T infusion, possibly due to CAR T-related adverse events. Health utilities values were numerically higher in patients in a progression-free health state compared with those with progressive disease. Although the sample size is relatively small and follow-up is ongoing, these health utility values can be informative for current and future economic evaluations."

Study Citation	Quantitative Findings or Narrative Summary	Authors' Conclusions
	A disutility of 0.05 (SE = 0.04) at week 4 was associated with the timing of the CAR T-cell therapy–related toxicities.	
Faramand et al. (2019)[89]	**CRS, %** Grade 0 : 0 Grade 1 : 45 Grade 2 : 40 Grade 3 : 5 Grade 4: 0 Grade 5: NR, but patients with grade 5 CRS had higher levels of IL-6, and angiopoietin 2/angiopoietin 1 ratio at day 1, which correlated with severe toxicity **Death due to severe toxicity, n (%):** 2 (10)	"In this analysis of 20 patients, we observed a correlation between severe CRS and elevated serum cytokine levels of IL-6 and ANG2/ANG1 ratio at day one suggesting that these biomarkers may be utilized to predict severe toxicity in patients treated with axicabtagene ciloleucel. While this study is limited by small sample size, our observations correlate with previously published biomarkers data in patients enrolled in clinical trials."
Nahas et al. (2019)[90]	**PCTT, n (%):** 6 (46) **Recovered ANC by day +42, n:** 0 **Platelets of 50,000/mL or less on the first day of lymphodepleting chemotherapy was a predictor of PCTT:** 5 of 6 PCTT patients (*P* = 0.01) **CRS grade ≥ 2 requiring tocilizumab, n/N (%)** Patients with PCTT: 4/6 (66.7) Patients without PCTT: 1/7 (14)	"Low platelet count at the first day of lymphodepleting chemotherapy may be an indicator of low stem cell reserve and a predictor for PCTT after axicabtagene ciloleucel. In addition, early onset of at least Grade 2 CRS may contribute to PCTT after axicel. Notably, 5 of 6 patients who went on to develop PCTT would have been excluded from participation in the ZUMA-1 registration trial."
Byrne et al. (2019)[76]	**Reasons for ineligibility, n** Death: 6 Transfer to another institution: 2 Clinical decline: 1 Loss of follow-up: 1 **Median time to ineligibility, days:** 54.8 (9 to 91) **Mean time waiting for reimbursement approval (waiting patients only), days**: 47.3 (5 to 166) **Time to treatment, days** Non-ZUMA-1: 77.5 ZUMA-1: 31.8 *P* = 0.003	"This single-center experience highlights the ongoing challenges with axicabtagene ciloleucel in the real world setting compared with the experience on ZUMA-1, including delays in insurance approval, use of bridging chemotherapy, added chemotherapy toxicity, and increased mortality while awaiting treatment. Standardized reimbursement pathways are needed to ensure timely access to these therapies."

Study Citation	Quantitative Findings or Narrative Summary	Authors' Conclusions
	Steroid use, % Non-ZUMA-1: 37.5 ZUMA-1: 40.0 **Tocilizumab use, %** Non-ZUMA-1: 62.5 ZUMA-1: 40.0 (NS) **Response by day 30, n (%)** **Non-ZUMA-1** CR: 3 (38) PR: 2 (25) SD: 1 (13) PD: 2 (25) **ZUMA-1** CR: 5 (100) **Survival, patients alive, n (%)** Non-ZUMA-1: 7 (88), after median follow-up of 78.5 days ZUMA-1: 5 (100%) after median follow-up of 721 days **Compared with being untreated** Median OS Non-ZUMA-1: Not reached Untreated: 61 days (*P* = 0.01)	
Maakaron et al. (2019)[92]	**CRS, grade ≥ 1, %:** 100 **CRS duration, median, days:** 6 **CRS, grade ≥ 2, n (%):** 22 (73.3) **Fever, %:** 100 Median maximal temperature, °C: 39.5 Fever duration, days: 5 Median time until onset, days: 1 **Neutrophil count, median on day of first fever /µL:** 1,475	"PCT was checked per the treating team's discretion and the trend was not followed for most of these patients. We herein hypothesize that PCT does not follow the same kinetics of other inflammatory markers frequently interrogated and may serve as a way to distinguish infection from CRS in this population, where 100% of patients experienced CRS and fevers, but 40% had normal PCT levels. The utility of PCT in antibiotic stewardship and the cut-off of 0.5 ng/mL should be further explored to guide antibiotic use in this population."

Study Citation	Quantitative Findings or Narrative Summary	Authors' Conclusions
	ANC of less than 500/mm3 on the day of first fever, n (%): 8 (26.7) **IV antibiotics during admission, n (%):** 29 (97) **Levofloxacin prophylaxis, n (%):** 27 (90) **Infections** Positive blood cultures, n (%): 0 (0) C. difficile infection, n: 1 Invasive sinusitis with mucormycosis, n: 1 **Median PCT, ng/mL**: 0.86 Patients required vasopressors, n: 2 **Death, total, n (%):** 3 (10) **Death from PD, n:** 2 **Death from invasive fungal infection, n:** 1	

AE = adverse event; ANC = absolute neutrophil count; CAR = chimeric antigen receptor; CI = confidence interval; CR = complete response or complete remission; CRES = CAR-related encephalopathy syndrome; CRS = cytokine release syndrome; EQ-5D = EuroQol 5-Dimensions questionnaire; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FL = follicular lymphoma; ICU = intensive care unit; IPI = International Prognostic Index; ITT = intention-to-treat; IV = intravenous; NR = not reported; NE = neurologic events; NS = not significant; ORR = objective response rate; OS = overall survival; PCT = procalcitonin; PD = progressive disease; PR = partial response or partial remission; PRO = patient-reported outcomes; QoL = quality of life; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; r/r = relapsed or refractory; SD = stable disease.

Note: Not all abbreviations were defined within the abstracts.

Appendix 10: Comparison of Axicabtagene Ciloleucel to Salvage Chemotherapy (ZUMA-1 to SCHOLAR-1)

Background

The primary clinical review of axicabtagene ciloleucel consisted of all single-arm clinical trials and observational studies, providing no comparative data with other treatments. The objective of this appendix was to provide an overview and critical appraisal of the indirect evidence available of the comparative efficacy of axicabtagene ciloleucel vis-à-vis salvage chemotherapy for adults with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL).

1.0 SCHOLAR-1 STUDY

Aim

SCHOLAR-1 was a retrospective, patient-level, meta-analysis of clinical trials and observational studies on response rates and overall survival (OS) in patients with r/r DLBCL. The overall aim was to provide a more rigorous comparison for the response rate observed in the patient population studied in ZUMA-1, to support the assumption used for the historical control response rate in ZUMA-1, and to provide a re-estimate for OS in the r/r DLBCL/transformed follicular lymphoma (TFL)/ primary mediastinal large B-cell lymphoma (PMBCL) population. The main objectives were to:

- estimate the response rate to next line of chemotherapy in patients with r/r DLBCL, TFL, and PMBCL
- estimate the OS in patients with r/r DLBCL, TFL, and PMBCL.

Methods

Study Design

SCHOLAR-1 was a pooled retrospective meta-analysis of patients with refractory DLBCL and was comprised of observational data from two centres in the US (MD Anderson Cancer Center, and Mayo Clinic Lymphoma Specialized Program of Research Excellence of the University of Iowa) and data comprised from two phase III randomized clinical trials (the National Cancer Institute of Canada Cancer Trials Group randomized phase III study LY12; and the French Lymphoma Academic Research Organisation randomized phase III Collaborative Trial in Relapsed Aggressive Lymphoma [CORAL] study). Although a meta-analysis combining SCHOLAR-1 data with additional data from the literature was undertaken, for the purpose of this summary, only the data from SCHOLAR-1 was reviewed as these data were used in the comparison of axicabtagene ciloleucel to salvage chemotherapy. Details of the databases contributing to SCHOLAR-1 are found in Table 49.

Patient Eligibility

Patient-level data from each study or institution were included for patients who were determined to be refractory and had commenced the next line of systemic therapy for refractory disease as outlined in the ZUMA-1 trial. Refractory disease was defined as one of

the following: progressive disease as best response to any line of chemotherapy; stable disease (SD) as best response to four or more cycles of first-line or two cycles of later-line therapy; or relapse at 12 months or sooner following autologous stem cell transplant (SCT). Patients were also required to have received an anti-CD20 mAb, such as rituximab (unless disease was CD20–), and an anthracycline as one of their prior regimens.

Table 49: Databases Contributing to SCHOLAR-1

Institution	Database Type	Data Extraction Criteria	Outcomes Collected
MDACC	Retrospective database	Identified patients with: • best response of PD to second-line therapy • best response of SD to second-line therapy after at least 2 treatment cycles • relapse within 1 year of autologous SCT	Response to salvage therapy Survival
NCIC	Subset of a randomized clinical trial	Extracted a subset of data from the randomized, multi-centre, phase III LY12 study[a] Identified patients with: • best response of PD to first-line therapy • best response of SD to first-line therapy after at least 4 treatment cycles • best response of PD to second-line therapy given in LY12[a] • best response of SD to second-line therapy given in LY12[a] after at least 2 treatment cycles • relapse within 1 year of autologous SCT	Response to second-line salvage therapy Survival
Mayo/Iowa (Specialized Program of Research Excellence Lymphoma Database)	Retrospective database	Identified patients with: • best response of PD to any line therapy • best response of SD to first-line therapy after at least 4 treatment cycles of therapy • best response of SD to later-line (> 1) therapy after at least 2 cycles of therapy • relapse within 1 year of autologous SCT	Response to salvage therapy Survival
CORAL	Subset of randomized clinical trails	Extracted a subset of data from the randomized, multi-centre, phase III CORAL study;[b] identified patients with: • best response of PD to first-line therapy • best response of SD to first-line therapy after at least 4 treatment cycles	Response to second-line salvage therapy Response to third-line salvage therapy Survival

CORAL = Collaborative Trial in Relapsed Aggressive Lymphoma; MDACC = MD Anderson Cancer Center; NCIC = National Cancer Institute of Canada; PD = progressive disease; SCT = stem cell transplant; SD = stable disease.

[a] Randomized Comparison of Gemcitabine, Dexamethasone, and Cisplatin Versus Dexamethasone, Cytarabine, and Cisplatin Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed and Refractory Aggressive Lymphomas, Crump, JCO, 2014.

[b] Collaborative Trial in Relapsed Aggressive Lymphoma, Gisselbrecht et al., J Clin Oncol. 2010.

Patients with central nervous system (CNS) disease, those diagnosed prior to 2000, those receiving an allogeneic SCT prior to salvage chemotherapy in the refractory setting, and patients with a history of Burkitt lymphoma or Richter's transformation were excluded.

Collaborating institutions extracted and provided data to the manufacturer. The manufacturer subsequently reviewed the extracted results, and only those patients documented to meet all elements of the refractory definitions were included. No information

on the methods used to extract the data for the studies, nor the manufacturer's approach to the verification of the data, was provided.

Patients were further classified into refractory category subgroups based on the first time in the treatment course that they met the criteria for refractory status (primary refractory, refractory to second- or later-line therapy, and relapse at 12 months or less of autologous SCT).

Assessments

The end points in SCHOLAR-1 were response rate (RR), complete response (CR), and OS. It is unclear what time frame was used to assess RR and CR in the report; however, survival was assessed at six months, 12 months, and 24 months. For the two randomized studies, assessment of response to therapy for refractory disease was in accordance with the International Working Group's revised response criteria for malignant lymphoma as per local/central review. For the two retrospective databases, response was according to the investigator assessment (the specific assessment criteria were not available).

Covariates

Potential covariates of interest included:

- sex
- Eastern Cooperative Oncology Group (ECOG) category (zero to one versus two to four)
- International Prognostic Index risk score
  - low risk: zero to one
  - low–intermediate risk: two
  - high–intermediate risk: equal to or greater than three
- disease stage (I to II, III to IV)
- disease type (DLBCL versus TFL/PMBCL)
- region (North America, Europe)
- data source (clinical trial, retrospective database)
- year of diagnosis (2000 to 2005 versus later than 2005)
- refractory subgroup according to First Refractory Categorization (primary refractory, refractory to second- or later-line therapy, relapsed within 12 months of autologous SCT)
- refractory subgroup according to Last Refractory Categorization (primary refractory, refractory to second- or later-line therapy, relapsed within 12 months of autologous SCT)
- primary refractory (yes or no)
- refractory to two or more consecutive lines of therapy (yes or no)
- response to treatment of refractory disease
- incidence of autologous or allogeneic SCT at any time after determination of refractory status (yes or no).

With the exception of covariates measured after determination of refractory status (response to therapy for the treatment of refractory disease and incidence of autologous or allogeneic SCT at any time after determination of refractory disease), covariates were measured at time of randomization in the clinical trials or measured at time of diagnosis for the observational data.

With respect to the refractory subgroup, as patients may have been refractory to therapy at multiple times throughout the treatment course, two different subgroup classifications were used. First Refractory Categorization was based on the refractory status at the first time in

the treatment course that the patient was determined to be refractory. The Last Refractory Categorization was based on the refractory status at the last time in the treatment course that the patient was determined to be refractory. For pooled analyses within SCHOLAR-1 only, the former definition was used; however, the Last Refractory Categorization was used for direct comparisons of SCHOLAR-1 with the ZUMA-1 study (standardized and propensity score [PS] analyses) (i.e., for the comparison between axicabtagene ciloleucel and salvage chemotherapy). In addition to these categorizations, patients were also classified as having ever been primary refractory or having been refractory to at least two consecutive lines of therapy at any point in the treatment course.

Analysis Populations

The analysis populations for SCHOLAR-1 are outlined in Table 50.

Table 50: Analysis Sets Used in SCHOLAR-1

Analysis Set	Description	Usage	Refractory Status Categorization	n
All extracted	The All Extracted Analysis Set consists of all patients transferred to Manufacturer from the participating institutions.	Data disposition and patient accountability	First	861
SCHOLAR- 1–evaluable	The SCHOLAR-1–evaluable analysis set consists of the subset of the All Extracted Analysis Set of patients who meet refractory criteria and who have evidence (an agent name and start date) of receiving salvage therapy for the treatment of refractory disease.	Demographic and disease characteristics	First Last	636 593
RR–evaluable	The RR–evaluable analysis set consists of the subset of the SCHOLAR-1–evaluable analysis set who have a disease assessment after receiving salvage therapy for the treatment of refractory disease.	RR Complete RR	First Last	523 508
Survival	The survival analysis set consists of the subset of the SCHOLAR-1-evaluable analysis set who have a reported survival status and date after receiving salvage therapy for the treatment of refractory disease.	Survival	First Last	603 497
Survival–RR	The survival–RR analysis set is the subset of patients in both the RR–evaluable and survival analysis sets.	Responder analyses of overall survival Sensitivity analyses of overall survival	First Last	513 497

RR = response rate.

Statistical Methods

All patients in the four databases meeting the inclusion criteria for SCHOLAR-1 were analyzed. No sample size calculations were performed. To combine the data from the four databases, patient-level meta-analytical techniques were used. Prior to estimation of the

RR, data in the RR–evaluable analysis set (defined in Table 50) were first assessed for homogeneity using the Higgins Q statistic[96] with a *P* value greater than 0.10 used to establish sufficient homogeneity of data to enable pooling of the data. [redacted]

OS was estimated from pooled patient record-level data in the survival analysis set using the Kaplan–Meier (KM) method. KM plots, the median survival time (95% confidence interval [CI]), and the survival rates at one and two years were estimated.

Although a number of additional analyses within each cohort and across patient and cohort characteristics were completed, for the purpose of this review of the SCHOLAR-1 study, only the results of the main effects for the overall group are presented.

Summary of SCHOLAR-1 Results

Data for 861 patient cases were transferred from participating institutions to the manufacturer, of which 636 patient cases were identified as meeting the inclusion criteria of First Refractory Categorization. The most common reason for case exclusion was lack of a documented therapy after determination of refractory status. Among these 636 patients, 523 (84%) were evaluable for response and 603 (95%) were evaluable for survival. Only [redacted] patients were common between the two analyses (i.e., were evaluable for both).

When applying the Last Refractory Categorization, [redacted], 508 [redacted] were evaluable for response, 497 [redacted] were evaluable for survival, [redacted]. The patient characteristics in the SCHOLAR-evaluable set are found in Table 51.

Table 51: Patient Characteristics of SCHOLAR-1

	Overall (N = 636)
Type of Data Source, n (%)	
Clinical trial	389 (61.2)
Retrospective database	247 (38.8)
Region, n (%)	
Europe	170 (26.7)
North America	466 (73.3)
Sex, n (%)	
Female	229 (36.0)
Male	407 (64.0)
Age (years) at Determination of Refractory Status	
N	636
Median (Q1, Q3)	55.0 (45.0, 61.0)
Age category	
< 65	553 (87.0)
≥ 65	83 (13.1)

	Overall (N = 636)
Disease Type, n (%)	
DLBCL	552 (86.8)
PMBCL	14 (2.2)
TFL	27 (4.2)
Other, unknown, or missing	43 (6.8)
ECOG Performance Status, n (%)	
0 to 1	464 (73.0)
2 to 4	87 (13.7)
Unavailable or missing	85 (13.4)
IPI Risk Classification, n (%)	
Low risk (0 to 1 points)	159 (25.0)
Low–intermediate risk (2 points)	152 (23.9)
High–intermediate to high risk (≥ 3 points)[a]	210 (33.0)
Missing or incompletely assessed	115 (18.1)
Disease Stage, n (%)	
I to II	174 (27.4)
III to IV	460 (72.3)
Missing	2 (0.3)
Number of Chemotherapy Regimens	
n	518
Median (Q1, Q3)	4.0 (3.0, 5.0)
Min., Max.	2, 26
First Refractory Subgroup, n (%)	
Primary refractory	180 (28.3)
Refractory to second or later therapy	315 (49.5)
Relapse after autologous SCT	141 (22.2)
Last Refractory Subgroup, n (%)	
Primary refractory	101 (20)
Refractory to second or later therapy	316 (62)
Relapse after autologous SCT	91 (18)
Primary Refractory at Least Once, n (%)	
Yes	257 (40.4)
No	[redacted]
Refractory to Any 2 Consecutive Lines of Therapy, n (%)	
Yes	321 (50.5)
No	[redacted]
SCT Prior to Determination of Refractory Status, n (%)	
Yes	146 (23.0)
No	[redacted]
SCT After Determination of Refractory Status, n (%)	
Yes	180 (28.3)
No	[redacted]

	Overall (N = 636)
Total Number of Lines of Chemotherapy and Autologous SCT Received, n (%)	
1	180 (28.3)
2 to 3	314 (49.4)
≥ 4	1 (0.2)

DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; Max. = maximum; Min. = minimum; PMBCL = primary mediastinal large B-cell lymphoma; Q1 = quartile 1; Q3 = quartile 3; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

[a] Three patients were confirmed to have IPI 5 (two from the Mayo Clinic Lymphoma Specialized Program of Research Excellence data and one from the MD Anderson Cancer Center data).

Source: Crump et al. 2017,[8] and National Institute for Health and Care Excellence.[80]

Estimation of Response Rate and Complete Response

There were 523 patients in the RR–evaluable analysis set, 135 (25.8%) of whom responded to therapy for refractory disease. The DerSimonian–Laird pooled estimate of RR was 26% (95% CI, 21% to 31%). There were 45 patients (8.6%) who attained a CR to therapy for refractory disease, for a pooled estimated CR rate of 7% (95% CI, 3% to 15%).

Estimation of Overall Survival

Among the 603 survival–evaluable patients, 505 patients (84%) died during follow-up. The median survival was 6.3 months (95% CI, 5.9 months to 7.0 months), with six-month, one-year, and two-year survival rates of 53% ([redacted]); 28% (95% CI, 25% to 32%) and 20% (95% CI, 16% to 23%), respectively.

2.0 SCHOLAR-1 Standardized Analyses to ZUMA-1 at Six Months and 12 Months

Background

While patients in the SCHOLAR-1 study met the criteria for r/r disease similar to patients included in the ZUMA-1 study, naïve, direct comparison between the results of SCHOLAR-1 and ZUMA-1 to assess the efficacy of axicabtagene ciloleucel relative to salvage chemotherapy may be biased due to the potential for imbalances in the patient populations related to differences in other characteristics and study inclusion criteria. Indeed, the SCHOLAR-1 database includes patients from both retrospective databases (i.e., patients were not enrolled in clinical trials) and from clinical studies in North America and Europe. The inclusion of non-trial patients in SCHOLAR-1 may lead to differences between ZUMA-1 and SCHOLAR-1 in the proportions of patients in different prognostic categories that predict study end points. Moreover, although patients were also included in SCHOLAR-1 from clinical trials, these patients may also not be fully balanced in all the important covariates (known and unknown) to allow for direct comparisons to ZUMA-1. As a result, the manufacturer conducted standardized analyses of response and survival at six months to compare treatment outcomes. An updated statistical analysis addendum extended these analyses to use 12-month follow-up data.

Aim

The specific objectives were to:

- compare the estimated RR from SCHOLAR-1 to the RR observed in the ZUMA-1 primary analysis at six months
- compare the OS in r/r DLBCL, TFL, and PMBCL patients in SCHOLAR-1 to the OS of patients in the ZUMA-1 primary analysis at six months.
- [redacted]

Assessments

The following definitions were used in both the standardized and PS analyses that were used to compare the results of SCHOLAR-1 and ZUMA-1.

Response

[redacted]. For ZUMA-1, those patients with a best response of CR or PR according to the International Working Group's revised criteria for malignant lymphoma were classified as responders. Patients without a CR or PR were considered non-responders, including those who were not able to be evaluated due to death prior to the first disease assessment. A patient who had a best response of CR was classified as a complete responder. A patient in ZUMA-1 with an unconfirmed complete response was classified as a partial responder, but not a complete responder.

Overall Survival

For SCHOLAR-1, OS was defined as the time from the date of commencement of treatment for refractory disease to the date of death from any cause. OS for patients alive at last contact were censored at the last date known alive. For ZUMA-1, OS was defined as the time from the date of the axicabtagene ciloleucel infusion to the date of death from any cause. Patients who had not died by the analysis data cut-off date were censored at their last date known to be alive prior to the data cut-off date with the exception that patients known to be alive or determined to have died after the data cut-off date for each analysis were censored at the data cut-off date.

Statistical Methods

The standardization method described in Rothman et al. (2008, p. 49-50, 67-68)[97] was used to compare the study end points for ZUMA-1 to those for SCHOLAR-1. Covariates for use in the standardized analyses were selected a priori. Covariates important for both response and survival were considered for inclusion in the standardized analyses and a limited number of strata were sought so that the number of patients in each stratum would be

sufficiently large to provide stable outcome estimates. [redacted]

[redacted]

Analyses for RR and CR were conducted in the modified intention-to-treat (mITT) analysis set for ZUMA-1 (i.e., all subjects treated with at least 1.0 x 10^6 anti-CD19 chimeric antigen receptor [CAR] T cells/kg) and the response analysis set for SCHOLAR-1. [redacted]

For the ZUMA-1 mITT analysis set and for the SCHOLAR-1 survival analysis set, the within-stratum KM median OS estimates in months and 95% CIs were calculated. Standardized estimates of survival, including median (95% CI), and six- and 12-month rates, were obtained using the same pre-specified stratifying covariates. The within-stratum median and six- and 12-month KM estimates were estimated. For survival measures, the standardized estimates from SCHOLAR-1 were obtained by estimating overall bootstrap samples across all strata where the number of samples within strata was weighted by the proportions of patients within each stratum in ZUMA-1.

[redacted]

Summary of Results: Axicabtagene Ciloleucel Comparison to Salvage Chemotherapy

Demographic and disease characteristics for patients in the ZUMA-1 and SCHOLAR-1 studies are provided in Table 52. The patients were generally balanced between ZUMA-1 and SCHOLAR-1 based on sex; however, notable differences were observed in almost all other variables. Overall, ZUMA-1 had a larger proportion of patients aged 65 years or older, a higher proportion of patients with late-stage disease, a higher proportion of patients with less favourable International Prognostic Index (IPI) scores, a larger proportion having TFL or PMBCL, and a higher proportion refractory to second-line or later, and more total number of lines of chemotherapy received. SCHOLAR-1 included patients with ECOG performance status of two to four, while ZUMA-1 only included those with an ECOG performance status of zero or one, based on ZUMA-1's inclusion criteria. A larger proportion of SCHOLAR-1 patients were primary refractory, [redacted]. A larger proportion of SCHOLAR-1 patients were refractory to at least two consecutive lines of therapy. Additionally, more patients in SCHOLAR-1 underwent SCT at some point after the determination of refractory status than patients in ZUMA-1. Importantly, a significant amount of data was missing from the SCHOLAR-1 patients with respect to ECOG performance status, IPI scores, disease stage, and number of lines of chemotherapy, making assessment of balance on these characteristics problematic.

Table 52: Patient and Disease Characteristics in ZUMA-1 (Modified Intention-to-Treat Analysis Set) and SCHOLAR-1 (Response and Survival Analysis Sets)

	ZUMA-1 mITT (N = 101)	SCHOLAR-1 Response (N = 508)	SCHOLAR-1 Survival (N = 497)
Sex			
N	101	508	497
Female	33 (33)	[redacted]	[redacted]
Male	68 (67)	327 (64)	321 (65)
Age (years)			
N	101	508	497
Median (min., max.)	58.0 (23, 76)	55.0 (19, 81)	55.0 (19, 81)
< 65 years	77 (76)	434 (85)	428 (86)

	ZUMA-1 mITT (N = 101)	SCHOLAR-1 Response (N = 508)	SCHOLAR-1 Survival (N = 497)
≥ 65 years	24 (24)	74 (15)	69 (14)
ECOG Performance Status			
N	101	288	281
0 to 1, n (%)	101 (100)	230 (80)	226 (80)
2 to 4, n (%)	0	58 (20)	55 (20)
Not assessed	0	220	216
IPI Score			
N	101	215	215
0 to 1, n (%)	27 (27)	73 (34)	73 (34)
2, n (%)	26 (26)	66 (31)	66 (31)
≥ 3, n (%)	48 (48)	76 (35)	76 (35)
Not assessed	0	293	282
Disease Stage			
N	101	224	224
I to II, n (%)	15 (15)	75 (33)	75 (33)
III to IV, n (%)	86 (85)	149 (67)	149 (67)
Not assessed	0	284	273
Disease Type			
N	101	508	497
DLBCL, n (%)	77 (76)	447 (88)	436 (88)
TFL/PMBCL, n (%)	24 (24)	20 (4)	20 (4)
Other, n (%)	0	35 (7)	35 (7)
Missing, indeterminate, or unknown, n (%)	0	6 (1)	6 (1)
Region			
N	101	508	497
Europe/Israel, n (%)	1 (1)	170 (33)	170 (34)
North America, n (%)	100 (99)	338 (67)	327 (66)
Data Source			
N	101	508	497
Clinical trial, n (%)	101 (100)	262 (52)	262 (53)
Retrospective database, n (%)	0	246 (48)	235 (47)
Total Number of Lines of Chemotherapy and Autologous SCT Received			
N	101	417	410
1, n (%)	2 (2)	101 (24)	100 (24)
2, n (%)	29 (29)	206 (49)	204 (50)
3, n (%)	30 (30)	94 (23)	91 (22)

	ZUMA-1 mITT (N = 101)	SCHOLAR-1 Response (N = 508)	SCHOLAR-1 Survival (N = 497)
4, n (%)	28 (28)	12 (3)	11 (3)
5, n (%)	6 (6)	1 (0)	1 (0)
> 5, n (%)	6 (6)	3 (1)	3 (1)
Not assessed	0	91	87
Refractory Subgroup			
N	101	508	497
Primary refractory, n (%)	2 (2)	101 (20)	100 (20)
Refractory to second or later line, n (%)	78 (77)	316 (62)	310 (62)
Relapse within 12 months of autologous SCT, n (%)	21 (21)	91 (18)	87 (18)
Primary Refractory at least once			
N	101	508	497
No, n (%)	75 (74)	277 (55)	267 (54)
Yes, n (%)	26 (26)	231 (45)	230 (46)
Refractory to at Least 2 Consecutive Lines of Therapy			
N	101	508	497
No, n (%)	47 (47)	193 (38)	187 (38)
Yes, n (%)	54 (53)	315 (62)	310 (62)
Autologous or Allogeneic SCT at Any Time After Determination of Refractory Status			
N	101	508	497
No, n (%)	90 (89)	347 (68)	336 (68)
Yes, n (%)	11 (11)	161 (32)	161 (32)

DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; PMBCL = primary mediastinal large B-cell lymphoma; SCT = stem cell transplant; TFL = transformed follicular lymphoma.

Source: European Medicines Agency.[18]

Standardized Estimates and Comparisons of Response

The standardized estimates of response and CR are provided in Table 53. After stratifying the refractory subgroup based on the Last Refractory Categorization, the standardized estimates of RR and CR were 20% and [redacted], respectively, for salvage chemotherapy in SCHOLAR-1. Standardized differences between axicabtagene ciloleucel and salvage chemotherapy were [redacted] for RR and CR (95% CI not reported), respectively, resulting in standardized ratios of 3.8 and 8.0, respectively.

Table 53: Standardized Comparisons of Response and Complete Response in ZUMA-1 (Modified Intention-to-Treat) and SCHOLAR-1 (Response)

	Axicabtagene Ciloleucel (ZUMA-1) mITT (N = 101)	Salvage Chemotherapy (SCHOLAR-1) Response (N = 508)	Standardized[a] Difference (95% CI)	Standardized[a] Ratio (95% CI)	Odds Ratio (*P* Value[b])
Response rate (6-month analysis)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complete response rate (6-month analysis)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Response rate (12-month analysis)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complete response rate (12-month analysis)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; mITT = modified intention-to-treat; SCT = stem cell transplant.

[a] Standardized according to pre-specified stratification factors of refractory group and autologous SCT or allogeneic SCT after determination of refractory disease.

[b] Cochran–Mantel–Haenszel test stratified based on pre-specified stratification factors.

[redacted]

Source: Manufacturer-submitted materials.[82]

The standardized estimates of survival at six and 12 months are provided in Table 54, and a KM plot for axicabtagene ciloleucel from ZUMA-1 and salvage chemotherapy from SCHOLAR-1 survival is provided in Figure 6. The standardized estimate of median OS for salvage chemotherapy [redacted]. Six- and 12-month survival rates were [redacted], for salvage chemotherapy. Of note, no median OS was calculable for axicabtagene ciloleucel from ZUMA-1 as the median survival was not yet reached in this study. The hazard ratio from the Cox model stratified by the pre-specified covariates was [redacted]).

Table 54: Standardized Estimates of Survival at Six Months and 12 Months for ZUMA-1 and SCHOLAR-1 (SCHOLAR-1 Survival–RR Analysis, ZUMA-1 mITT Analysis Set)

	Axicabtagene Ciloleucel (ZUMA-1) mITT (n = 101)	Salvage Chemotherapy (SCHOLAR-1) Survival (n = 497)	Standardized Difference/Ratio (95% CI)
Median OS (months)	[redacted]	[redacted]	[redacted]
6-month survival rate	[redacted]	[redacted]	[redacted]
12-month survival rate	[redacted]	[redacted]	[redacted]
Stratified Cox model		[redacted]	

CI = confidence interval; mITT = modified intention-to-treat; RR = response rate; stem cell transplant.

Note: In patients undergoing autologous SCT, survival time is derived from the time of SCT to death or date last known alive; therefore, the survival reported in this summary may differ from that reported in the ZUMA-1 Clinical Study Report.

Source: Manufacturer-submitted materials.[82]

Figure 6: Overall Survival, ZUMA-1 and SCHOLAR-1 (SCHOLAR-1 Survival–Response Rate Analysis, ZUMA-1 Modified Intention-to-Treat Analysis Set)

Source: Manufacturer-submitted materials.[82]

In sensitivity analyses, standardizing based on refractory and ECOG performance status strata provided similar results as the main findings, with standardized estimates of RR and CR of [redacted] respectively, for salvage therapy from the SCHOLAR-1 study. Standardizing based on refractory and ECOG performance status strata provided standardized median OS for the salvage chemotherapy from the SCHOLAR-1 study of 5.8 months, with six- and 12-month survival rates of [redacted]%, respectively. The standardized ratios of six- and 12-month survival rates are [redacted] months, respectively, and the hazard ratio from the Cox model stratified by the covariates used was [redacted] based on these sensitivity analyses.

3.0 Propensity Score Analyses of Comparison of ZUMA-1 With SCHOLAR-1 at Six Months and 12 Months

Background

In addition to standardized analyses as outlined previously, the manufacturer conducted several PS analyses to estimate the average treatment effect (ATE) if the ZUMA-1 RR and OS rates were applied to the historical controls obtained from the SCHOLAR-1 data.

Aim

The main objectives were to:

[redacted]

Methods

The specification of the PS followed conventional approaches whereby a set of predictors (i.e., covariates outlined as follows) were used to predict the probability of assignment to axicabtagene ciloleucel (ZUMA-1) or salvage chemotherapy (SCHOLAR-1), using a logistic regression model.

Covariates

[redacted]

Table 55: Analysis Subset for SCHOLAR-1 and ZUMA-1

	Union of SSAP1 Sets		Additional Data Subsetting
	ZUMA-1	SCHOLAR	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Source: Manufacturer-submitted materials.[82]

Propensity Score Development

The PS is the predicted probability from a logistic regression model that a patient receives the treatment (i.e., axicabtagene ciloleucel versus salvage chemotherapy) given the potential confounders included as outlined in Table 55. [redacted]

[redacted]

[redacted]

[redacted]

Results

Average Treatment Effects and Differences for Response Rate and Complete Response

The ATEs and differences for RR and CR after PS adjustments are provided in Table 56. The estimates of RR and CR rates with axicabtagene ciloleucel therapy (ZUMA-1) were [redacted], respectively and [redacted] with salvage therapy (SCHOLAR-1).

Table 56: Average Treatment Effects and Differences for Response Rate and Complete Response for Response 600 Set

	N	Axicabtagene Ciloleucel ZUMA-1 (%)	Salvage Chemotherapy SCHOLAR-1 (%)	Difference (95% CI)
Response 600				
RR	[redacted]	[redacted]	[redacted]	[redacted]
CR	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CR = complete response; RR = response rate.

Source: Manufacturer-submitted materials.[82]

Average Treatment Effect for Overall Survival and Overall Survival Hazard Ratios

The ATEs and differences, median OS and OS rates, and the hazard ratio for treatment with axicabtagene ciloleucel (ZUMA-1) versus salvage therapy (SCHOLAR-1) are provided in Table 57. [redacted]

Table 57: Average Treatment Effects and Differences, Median Overall Survival and Overall Survival Rates, and the Hazard Ratio for Treatment (Survival 600 Set)

	N	Axicabtagene Ciloleucel ZUMA-1	Salvage Chemotherapy SCHOLAR-1	Difference/Ratio (95% CI)
Median OS (months)	[redacted]	[redacted]	[redacted]	[redacted]
6-month survival rate (%)		[redacted]	[redacted]	[redacted]
12-month survival rate (%)		[redacted]	[redacted]	[redacted]
Hazard ratio[a]				[redacted]

CI = confidence interval; OS = overall survival.

[a] The hazard ratios are calculated with the stratified estimator on the common support data sets. The medians and survival rates are calculated with the doubly robust estimator of the treatment-specific survival functions.

Source: Manufacturer-submitted materials.[82]

4.0 Limitations

Limitations of SCHOLAR-1

The methods employed for the meta-analysis were appropriate with the use of random-effects models. However, the inclusion of both randomized controlled trial data and retrospective data in the SCHOLAR-1 databases and subsequently within the meta-analysis may be problematic as a number of differences in inclusion criteria, data collection, and assessments were noted.

First, the inclusion criteria for entry into the four studies that comprised the SCHOLAR-1 database were different. For IA/MC, LY12, and CORAL, patients were included at the first

instance of meeting refractory criteria, whereas for the MD Anderson Cancer Center study, patients who first met refractory criteria from second-line therapy onward were included.

[redacted]

Third, clinical differences in severity of disease were noted between the patients from the clinical trials versus the database cohorts. The patients included in the retrospective database had higher disease stage (III to IV) and fewer patients with IPI scores of zero to one relative to the clinical trial patients, suggesting that the retrospective database patients were sicker compared with the clinical trial patients.

Fourth, there were clear differences among the studies on the definitions used to define response and when those assessments occurred. Assessments response to therapy for refractory disease was determined by the 1999 International Working Group response criteria per local review for clinical trials included in SCHOLAR-1. Response to therapy for the retrospective database cohorts of SCHOLAR-1 was determined by the investigator assessment. Although the impact on results is unclear, it is possible that the criteria were applied more rigorously within the clinical trials as opposed to the individual investigators within the observational cohorts. Moreover, there were important differences in assessments between the cohorts. In the clinical trials, patients determined to be refractory were assessed for survival — approximately every three months for one year and then every six months for three years in CORAL and at least annually for LY12 as per protocol. For the retrospective database studies, patients were followed up for disease response and survival per institution standard procedures, which may have differed between institutions. Patients who were alive at the time of data extraction were censored at the date of last contact for the retrospective database studies. Given the relatively short follow-up in these studies, these differences in the timing of assessments may impact the estimated OS and hazard ratios in the pooled analyses.

Collectively, given the differences outlined earlier, clinical heterogeneity was likely a concern as differences in characteristics, prognostic factors, and outcomes were noted between the four cohorts of patients included in SCHOLAR-1. Indeed, subgroup analyses by individual cohorts as well as by characteristics also demonstrated a wide range results, suggesting clinical heterogeneity existed. However, no statistical heterogeneity in outcomes was observed based on the Higgins Q statistic, although the potential impact of inconsistency across studies and the potential impact on the meta-analysis results would have been better supported with the use of the I^2 statistic.[96]

Comparisons of SCHOLAR-1 to ZUMA-1

Although the previously noted limitations of the SCHOLAR-1 meta-analysis may be less important for the SCHOLAR-1 study results alone, these limitations have implications for the indirect comparison of axicabtagene ciloleucel to salvage chemotherapy. The meta-analysis of SCHOLAR-1 was based on the first refractory categorization, whereas the standardized and PS analyses, in which axicabtagene ciloleucel was compared with salvage chemotherapy, were based on the last refractory categorization. Although the number of

patients included did not change substantially between the first and last refractory categorizations with respect to RR and CR analyses [redacted]

Although it appeared that pooling of the data from the SCHOLAR-1 studies was appropriate for the RR, CR, and OS sets from a statistical perspective, it is unclear if this would also be the case for the select subsets that were eventually used to compare SCHOLAR-1 to ZUMA-1, particularly for end points related to OS. Indeed, the reduction in sample size from the original SCHOLAR-1 analyses to the standardized and PS analyses was not consistent across the clinical trial and retrospective database in SCHOLAR-1. [redacted] Whether these differences were sufficient to introduce significant heterogeneity into the pooled data are unknown, and this should have been formerly explored in the standardized or PS analysis. However, as noted earlier, retrospective database patients tended to have higher disease stages and fewer patients with IPI scores, lower overall RRs, and lower OS. It is possible that these subsets were a sicker population than originally presented within the SCHOLAR-1 study. Thus, failure to adequately control source of data, IPI scores, and disease stage in the standardized or PS analyses may have biased the study results. Although further restrictions were implemented to account for some of these important covariates (e.g., response 300, 200), this may have further introduced bias to the highly restricted samples analyzed.

There are also concerns about whether SCHOLAR-1 studies adequately reflect current contemporary practice to be considered an appropriate historical control. Although the exact years of patient inclusion in the meta-analysis are not specified, [redacted] Moreover, even though OS may not have changed significantly, the rate at which patients die may have changed due to changes in the natural history of the disease and improvements in best supportive care, which would significantly influence both the KM estimates and the hazard ratio estimates that rely on time to event within the historical controls.

The major issues highlighted earlier in the limitations of the SCHOLAR-1 study all may have impacted the comparisons of axicabtagene ciloleucel to salvage chemotherapy in both the standardized and PS analyses — most notably, the definitions used to define the outcomes and when those assessments occurred. The definitions used to define RR, CR, and OS were different between ZUMA-1 and SCHOLAR-1. For example, OS is defined as the time from the date of commencement of therapy for refractory disease to the date of death from any cause. For ZUMA-1, OS was defined as the time from the date of the axicabtagene

ciloleucel infusion to the date of death from any cause. ZUMA-1 also had standardized assessment whereas SCHOLAR-1 was a mixture of standardized assessments in the clinical trials to investigator assessments of response in the retrospective database. How these differences in definitions and timing of assessments for end points affected the results is unknown; however, these factors could introduce bias in the results, particularly in the analyses of OS, which require appropriate classification of time to the event to generate valid unbiased estimates.

The most significant limitation of comparisons of axicabtagene ciloleucel with salvage chemotherapy is the considerable heterogeneity between the study populations in ZUMA-1 and SCHOLAR-1. Although the SCHOLAR-1 data were restricted to better align with the ZUMA-1 study population, major differences between the study populations of ZUMA-1 and SCHOLAR-1 remained, and differences were more pronounced in the four individual data sets included in SCHOLAR-1 itself. As previously noted, the population in SCHOLAR-1 included patients with primary refractory disease whereas patients in ZUMA-1 included patients with a higher number of previous treatments who were more likely to have advanced disease than those in SCHOLAR-1. Furthermore, unlike ZUMA-1 patients, the SCHOLAR-1 data contained a relatively large proportion of patients (almost 30%) who received autologous SCT for primary refractory DLBCL. According to the clinical expert, these patients would not have been eligible for axicabtagene ciloleucel therapy, as they had failed only one line of therapy prior to autologous SCT; as such, they would only have been considered eligible for axicabtagene ciloleucel if they had achieved less than a PR after second-line therapy (e.g., platinum-containing). ZUMA-1 patients also had a larger proportion of patients aged 65 years or older, more TFL or PMBCL, more refractory to second-line or later, and more total number of lines of chemotherapy received. SCHOLAR-1 included patients with ECOG performance status scores of two to four, while ZUMA-1 did not. Importantly, a significant amount of data was missing from the SCHOLAR-1 patients with respect to ECOG performance status, IPI scores, disease stage, and number of lines of chemotherapy, making assessment of balance and control of these important confounders impossible. To account for the significant heterogeneity and potential confounding on estimates between the populations, the manufacturer completed standardized and PS analyses.

The standardized analyses used appropriate methods, particularly for data sets with small numbers where small or zero cells may be expected within strata, as was the case with ZUMA-1. However, to ensure standardized analyses are unbiased, the strata used in the standardization process must be based on confounding covariates that predict the study end points and for which the distribution of patients is not balanced between the control group (SCHOLAR-1) and treatment (ZUMA-1) group.[97] Based on results observed in the SCHOLAR-1 meta-analysis, the manufacturer determined that the proportion of patients in ZUMA-1 who fell into strata defined by refractory group and autologous or allogeneic SCT after determination of refractory disease was most important. However, these strata are unlikely to ensure complete balance between the groups as a number of other important confounders between the groups existed that were not accounted for in the determination of the strata or in the standardization process itself — most notably, IPI score, disease stage, and ECOG performance status. [redacted] Furthermore, the SCHOLAR-1 study enrolled patients who had ECOG performance status scores of two to four whereas ZUMA-1 was restricted to only patients

with ECOG performance status of zero to one. To control for this important confounding variable, the manufacturer completed two different standardized analyses from SCHOLAR-1. In the base case, patients with ECOG performance status greater than one were excluded to align with the criteria of ZUMA-1; however, patients with missing ECOG performance status scores were not excluded. In response to concerns from the National Institute for Health and Care Excellence (NICE) over the analysis, the manufacturer completed a sensitivity analysis whereby patients with missing ECOG performance status scores were also excluded. [redacted] In addition, a number of other clinically important covariates or subgroups of patients were not accounted for in the analyses, such as cell of origin or the presence of chromosomal translocations involving BCL2 and C-MYC (double-hit lymphomas). Overall, given the limited strata used in the analyses to control for major confounders and the exclusion of other major confounders, it is unlikely that the standardized analyses resulted in sufficient balance between the groups. Therefore, bias in the estimates of axicabtagene ciloleucel (ZUMA-1) applied to SCHOLAR-1 historical controls would be expected.

To further address imbalances between SCHOLAR-1 and ZUMA-1 patients, the manufacturer completed two additional analyses based on PS methods. [redacted]. Although the rationale may be appropriate, it may also result in issues in specifying that all covariates be used in the PS model. Covariates that may predict the outcome but not necessarily the treatment per se, may not have been included. How this impacts the specification of the PS remains unknown.

More importantly, as noted previously, major confounders such as IPI scores, disease stage, ECOG performance status, and cell origin were also not included in the development of the PS due to a substantial number of patients missing these data in SCHOLAR-1. A number of additional covariates were also excluded from the PS development, such as source of data, any patient for whom the value of disease type was something other than DLBCL, PMBCL, or TFL, and those missing the number of lines of chemotherapy — all excluded from the SCHOLAR-1 data. The rationale for the exclusion of patients may have been necessary to generate PSs; however, these variables are likely important confounders and it is unlikely that the specification of the PS would have sufficiently balanced the ZUMA-1 patients and SCHOLAR-1 patients to ensure unbiased estimates of outcomes. Although the manufacturer completed additional analyses, which involved subsets of patients who did not have missing data on some of these covariates, the results should be interpreted with consideration of the limitations noted. The reduction in sample size is substantial. [redacted]

To ensure unbiased estimates with the use of PS, all major confounders — both those included in the PS development itself and other potential confounders — must be balanced. Overall, the reported balance diagnostic data were limited for the PS models. The authors indicated that because of the use of stratification on PS, the PS approach is similar to a

matched design. As a result, PS should be well balanced between the groups. Although there is no universally agreed-upon threshold to indicate balance, some sources state that standardized differences less than 0.1 would represent negligible differences.[98] In the stratified analyses, age, sex, and post-autologous SCT refractory status had standardized mean differences greater than 0.1. [redacted] Importantly, balance was only assessed on the six variables included in the PS model. However, heterogeneity was observed on almost all variables between ZUMA-1 patients and SCHOLAR-1 patients prior to specification of the PS. Given imbalances were noted among the six PS covariates, it cannot be concluded that balance is achieved in the covariates not included in the PS model. Moreover, other important balance diagnostic data were not reported, such as box plots, cumulative density plots, or the distribution of variables by quintile of PSs. The balance across the full range of patients and all-important subgroups of patients were not presented.

To further address the issue of residual confounding after specifying the PS, the manufacturer further included a covariate adjustment in the model based on the probability of achieving the outcome. Any imbalance in covariates using strata or IPW estimators was presumed to be fully balanced following regression adjustment. Thus, the stratification with regression adjustment was deemed sufficient to achieve balance between the groups, according to the manufacturer. However, whether balance was achieved after PS and regression adjustment was not empirically tested; thus, whether balance was fully achieved and how this may have affected the study results is uncertain. Moreover, although all 101 ZUMA-1 patients were included in the specification of the PS itself, [redacted]. Although trimming on PS is appropriate due to the small sample size of the ZUMA-1 population, the exclusion of a substantial number of ZUMA-1 patients may be problematic. How these patients relate to those included in the analyses in terms of characteristics and outcomes is unknown and exclusion of these patients may introduce bias into the analyses.

With regard to external validity, although clinical trial data from Canada was included in SCHOLAR-1 data, a significant amount of data was derived from retrospective databases in the US. It is likely that a number of important differences between the US and Canada exist concerning the management of these patients — most notably health insurance coverage, which would be expected to impact outcomes. While some social or economic differences are very likely to exist between patients treated in the US and Canada, the clinical expert does not expect this to contribute to any differences between disease and response characteristics. However, it should be noted that patients included in SCHOLAR-1 tended to be younger than typical patients observed in Canada.

Collectively, the results of the SCHOLAR-1 series of studies and comparison of effectiveness between axicabtagene ciloleucel and salvage chemotherapy should be interpreted with consideration given to the inherent limitations of each. A number of key limitations related to the selection and assessment of patients, as well as the standardized and PS methods, were identified that could potentially bias the results of the comparison between axicabtagene ciloleucel and salvage chemotherapy. First, fundamental differences between the clinical trials and retrospective database for inclusion in SCHOLAR-1 were noted, as were concerns over the assessment and timing of the major clinical end points. Second, and most importantly, clinically important heterogeneity was observed across all

major covariates between ZUMA-1 and SCHOLAR-1 patients, and the statistical analyses completed are unlikely to have accounted for all major differences. These major concerns were also noted by NICE.[99] NICE indicated that the standardization procedure was unlikely to account for all major confounders due to the exclusion of several notable covariates and limited number of strata on confounding variables. NICE also noted the generation of PSs did not include all-important potential confounders, particularly around disease severity, and may have been biased by the differential distribution of invalid or missing data between clinical trials and retrospective data sets within SCHOLAR-1 and between SCHOLAR-1 and ZUMA-1 groups. Finally, NICE noted that limited data were presented to support the authors' claims that the PS model was adequately specified and that patient characteristics were balanced between groups. The standardized mean differences were sufficiently high on several important confounders; however, the balance of confounders not included in the specification of the PS was not presented. Moreover, it is impossible to determine if the additional regression adjustment conducted by the manufacturer resulted in complete balance between SCHOLAR-1 and ZUMA-1 patients. PS methods can only control for measured confounders, and systematic differences may remain between the ZUMA-1 patients and those selected from SCHOLAR-1.

5.0 Conclusions

The primary clinical review of axicabtagene ciloleucel consisted of all single-arm clinical trials and observational studies, providing no comparative data with other treatments. The objective of this appendix was to provide an overview and critical appraisal of the indirect evidence available of the comparative efficacy of axicabtagene ciloleucel compared with salvage chemotherapy for adults with r/r DLBCL.

The SCHOLAR-1 series of studies aimed to provide a more rigorous comparison of response among the patient population studied in ZUMA-1, to support the assumption on the historical control RR in ZUMA-1 and to provide a rigorous estimate for OS in the refractory DLBCL/PMBCL/ TFL population. Compared with subsets of patients in the SCHOLAR-1 study, the potential treatment effect of axicabtagene ciloleucel based on the ZUMA-1 study was estimated to have an approximately fourfold higher RR, approximately fivefold to eightfold higher CR, and approximately threefold higher 12-month OS rate. These results may suggest that treatment with axicabtagene ciloleucel provides an improvement in RR, CR, and OS for patients with refractory DLBCL, PMBCL, and TFL; however, the potential for significant bias in the comparisons exists. There is considerable heterogeneity between the study populations of ZUMA-1 and SCHOLAR-1. These differences were unlikely to be accounted for with the statistical analyses employed. As NICE also indicated,[99] because of these substantial limitations, the magnitude of the benefit of axicabtagene ciloleucel compared with salvage chemotherapy remains unknown.

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

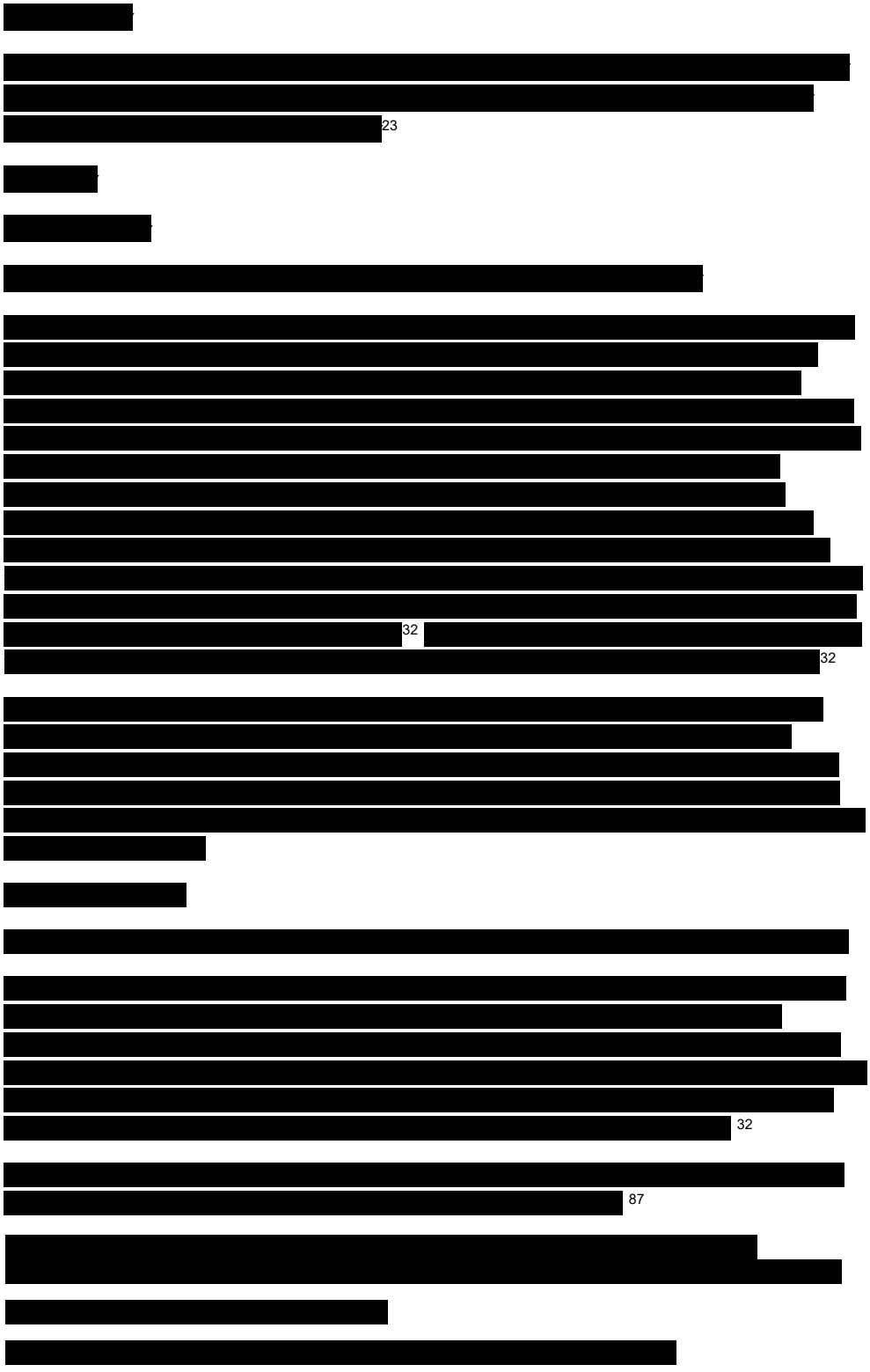
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted][81]


23
32
32
32
87

[redacted]

[redacted]

[redacted][100][redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted][81]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	

[redacted][31]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

[redacted]

[redacted]

[redacted]

[redacted] 81

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	

[redacted]

[redacted] [81]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted][101]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted][102] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1. [redacted] 100 [redacted]

[redacted]

[redacted]

[redacted]

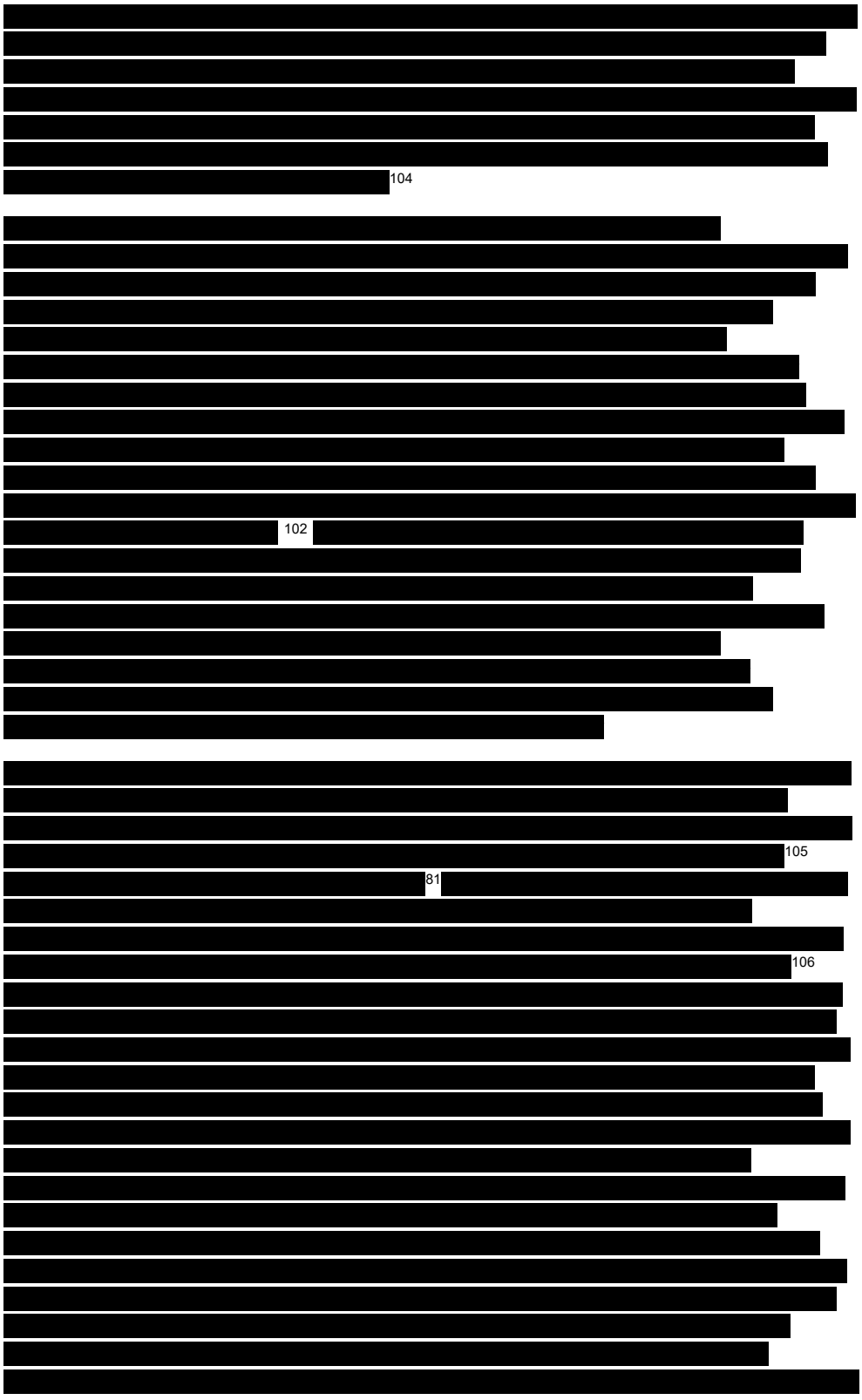
[redacted]

5. [redacted]

[redacted]

[redacted]

[redacted][8] [redacted]


104
102
105
81
106

[redacted]

Appendix 12: Ongoing Clinical Trials of Chimeric Antigen Receptor T-Cell Therapy

Table 64: Ongoing Clinical Trials of Chimeric Antigen Receptor T-Cell Therapy

Identifier	Study Name	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
NCT03761056[107]	Efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Participants With High-Risk Large B-Cell Lymphoma (ZUMA-12)	January 29, 2019, to August 2020	Phase II/ US	40	High-grade large B-cell lymphoma (18 or older)	Cyclophosphamide and fludarabine conditioning chemotherapy followed by axicabtagene ciloleucel	CR rate (up to 2 years)	• ORR • DOR (up to 15 years)
NCT03391466[108]	Efficacy of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7)	December 14, 2017, to January 2035	Phase III randomized, open-label, multi-centre study/ Austria, Belgium, Canada, France, Germany, Israel, Italy, Netherlands, Spain, Sweden, UK, US	350	DLBCL, relapsed or refractory disease after first-line chemo-immunotherapy (18 or older)	Axicabtagene ciloleucel (following conditioning chemotherapy regimen of fludarabine and cyclophosphamide) vs. standard of care (platinum-containing salvage chemotherapy followed by high-dose therapy and autologous stem cell transplant in responders)	Event-free survival (up to 5 years)	• ORR • OS (up to 5 years)
NCT03704298[109]	Safety and Efficacy of Axicabtagene Ciloleucel in Combination With Utomilumab in Adults	November 20, 2018, to June 2035	Phase I/ phase II multi-centre study/US	48	Chemo-refractory large B-cell lymphoma, including:	Axicabtagene ciloleucel plus utomilumab (following conditioning chemotherapy regimen of fludarabine and cyclophosphamide)	Phase I: Dose-limiting toxicities (up to 28 days)	• ORR • DOR • PFS • OS

Identifier	Study Name	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
	With Refractory Large B-cell Lymphoma (ZUMA-11)				• DLBCL not otherwise specified (ABC/GCB), • HGBCL with or without MYC and BCL2 and/or BCL6 rearrangement • DLBCL arising from follicular lymphoma • T-cell/histiocyte rich large B-cell lymphoma • DLBCL associated with chronic inflammation • Primary cutaneous DLBCL, leg type • EBV with DLBCL (18 or older)		Phase II: CR rate (up to 1 year)	(up to 15 years) • AEs • Changes in lab safety values (up to 24 months plus 30 days) • Levels of axicabtagene ciloleucel in blood • Levels of cytokines in serum (up to 2 years)
NCT02348216[38]	Safety and Efficacy of KTE-C19 in Adults With Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1)	January 2015 to October 2034	Phase I safety study, phase II pivotal study (cohort I and cohort II), and phase II safety management	290	• DLBCL, PMBCL, TFL, HGBCL • Chemotherapy-refractory disease (18 or older)	Axicabtagene ciloleucel (following conditioning chemotherapy regimen of fludarabine and cyclophosphamide)	Phase I: Dose-limiting toxicities (up to 30 days) Phase II Pivotal trial: ORR	• DOR • ORR • PFS (up to 12 months) • OS (up to 24 months) • AEs

Identifier	Study Name	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
			study (cohort III and cohort IV, cohort V and cohort VI), multi-centre/ Canada, France, Germany, Israel, Netherlands, US				Phase II safety management study: Incidence and severity of CRS and neurologic toxicities (up to 12 months)	• lab safety values • Percentage of participants with anti-axicabtagene ciloleucel antibodies • Levels of cytokines in serum (up to 12 months) • Levels of anti-CD19 CAR T cells in blood (up to 24 months) • Phase II safety management study only: • EQ-5D • VAS (up to 5 years)
NCT02926833[110]	Safety and Efficacy of KTE-C19 in Combination With Atezolizumab in Adults With Refractory Diffuse	September 2016 to August 2033 (primary outcome measure	Phase I/ phase II multi-centre study/ US	37	• DLBCL • Chemotherapy-refractory disease (18 or older)	Conditioning chemotherapy regimen (fludarabine and cyclophosphamide), followed by axicabtagene ciloleucel, followed by a	Phase I: Dose-limiting toxicities (21 days from first dose of atezolizumab)	• ORR • DOR • PFS • OS • AEs

Identifier	Study Name	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
	Large B-Cell Lymphoma (DLBCL) (ZUMA-6)	completed February 14, 2019)				limited course of atezolizumab	Phase II: CR rate (up to 5 years)	• lab safety values (up to 5 years) • Levels of axicabtagene ciloleucel in blood • Percentage of participants with anti-axicabtagene ciloleucel antibodies • Percentage of participants with anti-atezolizumab antibodies in serum • Levels of atezolizumab in serum • Levels of cytokines and other markers in serum (up to 2 years)

Identifier	Study Name	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
JPRN-JapicCTI-183914[111]	A Phase 2 Multicenter, Open-label, Single-arm Study of KTE-C19 in Japanese Patients with Refractory or Relapsed Large B Cell Lymphoma	April 2018 to NR	Phase II multi-centre, open-label, single-arm study/Japan	10	Refractory or relapsed (relapse after transplant or relapse after medication in patients ineligible for transplant) DLBCL, PMBCL, TFL or high-grade B-cell lymphoma (20 or older)	Axicabtagene ciloleucel	ORR by investigator	• ORR by central review • DOR • PFS • OS

ABC = activated B cell; AE = adverse event; CAR = chimeric antigen receptor; CR = complete response; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EBV = Epstein-Barr virus; EQ-5D = European Quality of Life Five Dimension Five Level Scale; GCB = germinal center B cell; HGBCL = high-grade B-cell lymphoma; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PMBCL = primary mediastinal large B-cell lymphoma; TFL = transformed follicular lymphoma; VAS = visual analogue scale.

Source: The trials were identified from ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform.